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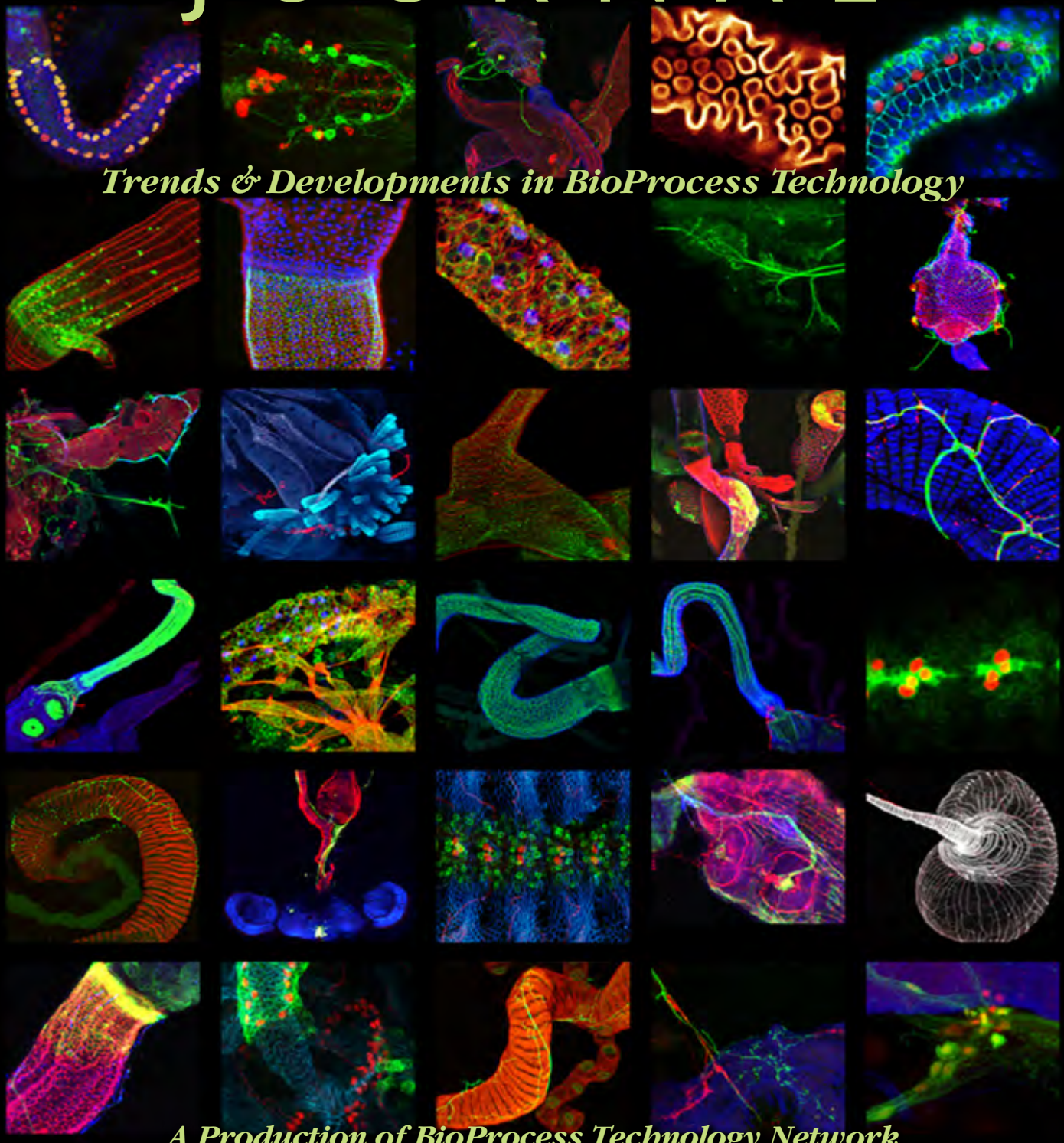

Trends & Developments in BioProcess Technology

A Production of BioProcess Technology Network

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TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Spinning Out: *From Concept to Actualization*

By ALLAN ROSETZSKY and CHARLOTTE DYRING

Introduction

This article is structured as a case study and describes the formation of ExpreS^{2}ion Biotechnologies (ExpreS^{2}ion). Few start-ups follow the exact same path and the launch of ExpreS^{2}ion was no exception. However, there are key elements identified in this article that are common to most biotech start-ups as well as supporting elements specific to this start-up.

The Start-Up Company

ExpreS^{2}ion, established in January 2010, is located in the Hørsholm Science Park, north of Copenhagen. It was formed as a spin-out from Affitech A/S (Affitech) which holds an equity position in the company. ExpreS^{2}ion operates as a contract research organization (CRO) offering services related to vector and cell line development, cloning, upstream development, optimization, and production of GLP material using its S2 (*Drosophila* Schneider 2*)* cell-based ExpreS^2 platform.

Two of the company's founders, Drs. de Jongh and Dyring, and early employees of ExpreS^{2}ion were colleagues for many years at Affitech and Pharmexa A/S (Pharmexa) before the two companies combined. It was during this period that they developed and optimized a S2 expression system for use in the production of therapeutic vaccines. ExpreS^{2}ion's proprietary protein expression platform, ExpreS^2, consists of high-yielding expression vectors, a S2 cell line that grows to higher cell densities than standard S2 cells, an optimized culture media, and a highly efficient transfection reagent specifically optimized for S2 cells.

Background Information on the Parent Company

In 1999, the Danish biotech company, Pharmexa, added S2 cells to its *E. coli* and mammalian cell protein expression platforms. Pharmexa's business goal was to develop therapeutic vaccines against various cancer and immunological indications using its proprietary AutoVac™ technology. Examples of proteins expressed by Pharmexa's S2 protein expression platform are shown in Table 1.

After the S2 cell lines were introduced, it quickly became clear that this platform outperformed the mammalian cell systems with respect to the expression of complex proteins at high levels. Thus, Pharmexa invested in the development of the S2-based platform including upstream and downstream processes and analytical tool techniques.

Merits of the Technology

The S2 cell system was shown to be useful for transient expression as well as for generating stable cell lines. This feature made it an excellent system for both research and product development by allowing one expression system to be used from the research bench through clinical material manufacturing.

A hallmark of the S2 system is the one-step gene amplification that occurs during selection, generating high-expressing cell lines without amplification. Further, the stability of polyclonal pools from the S2 cell system, in the absence of a selection agent, eliminates the step of clonal isolation during the discovery phase.

Within Pharmexa, the molecular biology and cell culture

TABLE 1. Election of complex proteins expressed by Pharmexa using the *Drosophila* S2 expression system.

Protein	Size (kDa)	S-S Bridges (#)	N-glycosylation Sites (#)
HER-2 (extracellular domain)	70.5	25	7
HA (H5N1, two chains)	70.0	5	5
EGFR (extracellular domain)	170.0	25	11-12

(MBCC) team, led by Dr. Dyring, was responsible for optimizing protocols and procedures as well as developing proprietary culture media, vectors, and a transfection reagent for S2 insect cell lines. In early 2008, Pharmexa management and the MBCC team discussed leveraging the full potential of the optimized S2 protein expression platform by creating a spin-off unit offering services and licenses to the S2 technology.

Parent Company as a Partner

Two key MBCC team members, Dr. Charlotte Dyring and Dr. Wian de Jongh, were tasked with preparing data and documents in support of the spin-off business plan. In December 2008, Pharmexa merged with the Norwegian company, Affitech. Following the merger, management decided that the S2 platform should remain in-house and be optimized for the production of antibodies, thus ending the spin-out effort. However, by September 2009, financial pressures brought about by the global recession intervened and Affitech made the decision to close down the Pharmexa portion of the company. However, the company continued to support the MBCC team's development activities through the end of 2009.

Despite the decision to close the Pharmexa unit, Affitech continued to support Drs. de Jongh and Dyring while they drafted a second spin-out business plan incorporating the S2 platform. By the time the two were prepared to launch ExpreS^{2}ion Biotechnologies, the S2 expression platform was ready for commercial use and elements of an investor-focused business plan were in hand. Affitech offered Drs. de Jongh and Dyring upstream equipment, together with office equipment and a significant amount of consumables from the Pharmexa portion of the company, as part of the spin-out package, provided that equity funding was secured within a pre-determined timeframe.

A Solid Founding Team

Forming a well-balanced founding team is always critical to securing equity funding. Investors carefully evaluate the strength of the founders by reviewing their backgrounds, experiences, and track records. Drs. de Jongh and Dyring were scientists with experience in department and project management. Dr. de Jongh had established a strong track record of success in expressing complex proteins considered difficult or nearly impossible to do. However, they still needed someone experienced in raising equity funding and starting new companies. They invited former Pharmexa colleague, Dr. Martin Roland Jensen, to join them. Dr. Jensen had started and operated several small biotech companies including the Danish company, CytoVac A/S (Cytovac), a cell-based, personalized therapy organization focused on research and clinical development.

Launching ExpreS^{2}ion Biotechnologies

Commencing Operations

Once the new spin-out became a reality in January 2010, they signed a collaboration agreement with Rhein Biotech, and then lined up their first commercial customer shortly thereafter. During this initial period, CSO and Managing Director, Dr. Dyring (now CEO), was the first founder to be fully employed by the company. VP of Product Development, Dr. De Jongh (now CSO), continued working to optimize the S2 expression system at Novo Nordisk Foundation Center for Protein Research for another year. Chairman of the Board, Dr. Jensen, remained as CEO for CytoVac. However, ExpreS^{2}ion hired a senior cell culture technician who had worked closely with Dr. Dyring for eight years at Pharmexa and Affitech on all aspects of the S2 cell system. This person immediately took over responsibility for setting up and running the ExpreS^{2}ion laboratories and working on customer projects.

ExpreS^{2}ion secured a grant to develop a malaria vaccine in collaboration with Copenhagen University (CU). This grant contributed significantly to ExpreS^{2}ion's early revenue stream. In the spring of 2010, Affitech offered to transfer intellectual property (IP) rights and equipment to ExpreS^{2}ion. In return, Affitech would be given 50% of ExpreS^{2}ion stock with the stipulation that ExpreS^{2}ion secure equity funding within six months.

Securing Equity Financing

Co-founders Dyring, de Jongh, and Jensen sought to identify investors with strategies that matched their business plan. After having presented to two Danish venture capitalists (VCs), the founders approached Vaekstfonden, a Danish state investment fund with a mandate to create new growth companies nationwide by providing venture capital and business expertise. They presented their business plan to Partnerkapital, a unit of Vaekstfonden. Partnerkapital's approach was to co-invest with angel investors who had relevant business experience. Partnerkapital joined with business angel, Allan Rosetzsky, MD, and an agreement was signed in September 2010.

ExpreS^{2}ion received 50% of the funding immediately, and another 25% was promised in 12 months after a series of milestones were met. The remaining 25% would be paid nine months later, also based on predefined accomplishments. The business plan called for the company to be fully self-supporting at the end of the investment period.

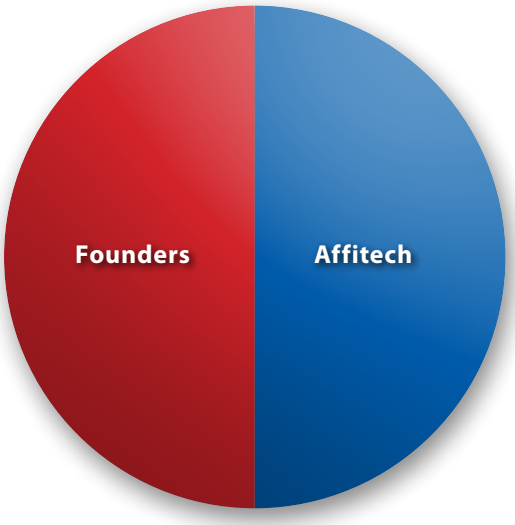

FIGURE 1. Ownership prior to the investment.

FIGURE 2. Ownership after the third tranche.

Company Ownership

Prior to the investment agreement, Affitech and the founders had each owned 50% of the ExpreS²ion shares (Figure 1). After the third tranche had been invested in spring 2012, the ownership distribution changed as shown in Figure 2. Each equity holder was represented on the board by one member, having one vote.

Critical Skill Requirements

As part of the investment agreement, Partnerkapital insisted that a senior sales and marketing/business development person be hired immediately to begin the process of generating CRO agreements. This type of background and skillset was deemed critical since the scientific founders lacked this expertise. Thus, Sancha Salgueiro, PhD, MBA, was hired by ExpreS²ion to serve as VP of business development. She is a molecular biologist who has worked in both start-up and established biotech organizations and has significant business training and experience.

Spending Controls

It was critical from the onset that ExpreS²ion prioritize which tasks: (a) should be performed in-house; (b) could be outsourced; and (c) would be set aside until a later time. At ExpreS²ion, the initial focus was on molecular biology, cell line and upstream process development, and simple analyses (*e.g.*, Western blotting). Because the build-out of a downstream lab was postponed for a time, purification requirements were outsourced. The company also outsourced such things as intellectual property, legal, bookkeeping, and auditing, on a case-by-case basis.

ExpreS²ion rented office, lab, and storage space in a modern start-up company incubator building equipped for protein production. The building housed five other companies that share meeting rooms, a canteen, and other facilities and services.

Key Personnel

The founders and key members of the ExpreS²ion team had already demonstrated a successful working

FIGURE 3.
The ExpreS²ion Biotechnologies team.

collaboration over their many years with the parent company. With a fully functioning team already in place, ExpreS²ion was able to take on protein expression contract work in the very earliest days of the company. ExpreS²ion also incorporated engineering students from the Technical University of Denmark into the operation. This combined team dynamic was invaluable in reaching projected milestones (Figure 3).

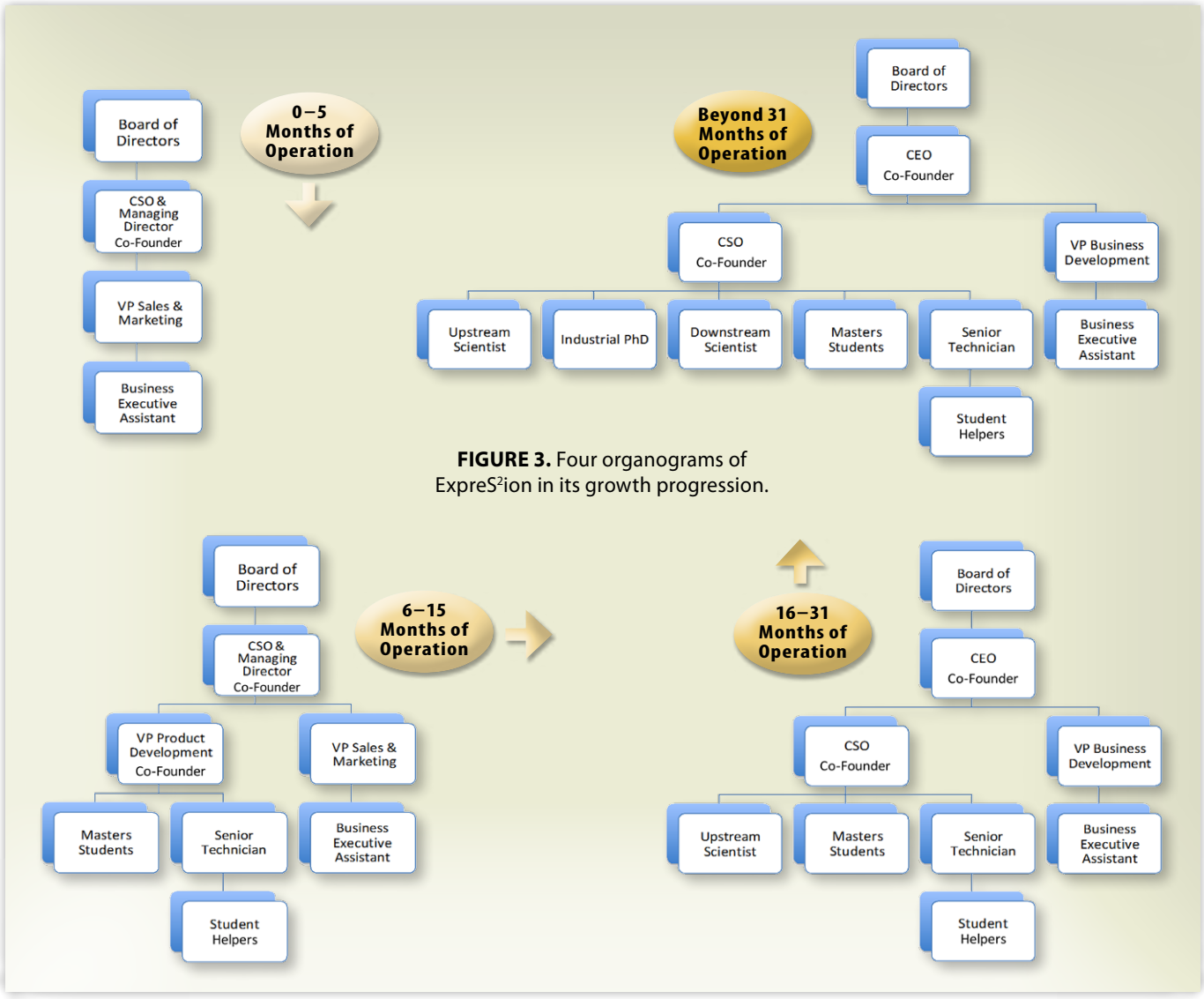

FIGURE 3. Four organograms of ExpreS²ion in its growth progression.

Summary

ExpreS²ion Biotechnologies' start-up experience has been a success. The company's business plan contained these basic elements necessary to attract equity investments:

- a balanced founding team that combined the developers of the S2 technology and an entrepreneur with relevant start-up experience;
- an identified industry need for an alternative protein expression-enabling approach; and
- a patent-protected platform technology for protein expression.

In addition, the ExpreS²ion Biotechnologies' founders were able to incorporate elements that surely strengthened their business plan:

- a parent company that supported late development work by offering IP as well as laboratory equipment, supplies, and furniture in exchange for an equity position;
- securing a customer project, a collaborative agreement, and a grant shortly after the formation of the company, all prior to securing an equity investment;

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- the opportunity to hire key personnel with in-depth S2 technology experience from the parent company right from the start; and
- an equity investment partnership that provided additional relevant business experience to the founding team.

ExpreS²ion Biotechnologies has been thriving for three years by offering services related to vector and cell line development, cloning, upstream development, optimization, and production of GLP material using the ExpreS² technology. ExpreS²ion can facilitate GMP production scale-up in collaboration with: (a) their preferred CMO partners; (b) the customer; or (c) the customer's preferred CMO. In addition, expression platform licenses are offered, and individual components (transfection reagents and culture media) can be obtained from the company.

Customers include Novartis Pharma, Hoffman-La Roche, Mucosis, and others. Grant collaborators include Copenhagen University, the Jenner Institute at Oxford University, and others. ExpreS²ion is also involved in a number of collaborations with service or equipment companies such as CELLution, Merck-Millipore, and Refine Technologies. ExpreS²ion is able to evaluate new equipment and techniques while the collaborating partners gain valuable information on how the equipment performs with S2 cells. In addition, the companies have the opportunity to co-market their products and technologies.

Two additional ExpreS²ion Biotechnologies articles have been published in the *BioProcessing Journal:*

Dyring C. Development of pregnancy-associated malaria vaccine using the ExpreS² insect cell expression system. *BioProcess J*, 2012; 11(3): 14-19.

Dyring C. Optimising the *Drosophila* S2 expression system for production of therapeutic vaccines. *BioProcess J*, 2011; 10(2): 28-35.

About the Authors

Allan Rosetzsky, MD, is member of the board of directors and assists with business negotiations, regulatory affairs, and developmental issues.

Charlotte Dyring, PhD, an expert in the *Drosophila* S2 expression technology, is the Chief Executive Officer and company co-founder.

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