This is the story of how a Swedish start-up came to set the standard for cell cultivation. This is who we are and where we come from.

Who, Why, When & Where ...

Father and son Tryggvason.
Photo: Håkan Lindgren.

The Father, the Son and the Holy Laminin Molecule

It all started back in Stockholm in 2008. Kristian Tryggvason, with a Ph.D. in molecular biology, having just finished an MBA, sat with his father Karl Tryggvason, Professor at Karolinska Institutet with a focus on extracellular matrix (ECM) proteins, to listen to a business proposal.

After years of unsuccessful attempts by many other groups, Karl had finally been able to produce full-length, human recombinant laminin proteins. As the foundation of the cell's basement membrane, laminins are the ECM proteins closest to the cell surface, which give them a vital biological role. In collaboration with his former colleague from Finland, Outi Hovatta, then serving as Professor and chief physician at the Fertility Unit of the Karolinska University Hospital in Huddinge, Sweden, they had discovered that Karl's laminin matrix could serve as an excellent defined substitute for feeder cells for pluripotent stem cell culture. In addition, they noticed that some of the laminin isoforms facilitated differentiation of the stem cells into cardiomyocytes, hepatocytes, retinal cells, insulin-producing cells, and neural cells.

From those first discoveries, Karl understood that he had invented an excellent research tool that potentially could facilitate the development of cell therapies. Karl's vision was clear. He wanted to build a cell therapy company with his son, Kristian, at its head.

"When my father presented his business idea to me, I directly saw the value of his innovation, the competitive advantage of these recombinant laminins, and how they would benefit the entire stem cell research field," says Kristian. "To put the Biolaminins in use also for basic research, the best route to enable cell therapies." >>

Read more about the laminin technology on page 22 >>

Kristian continues, "I always wanted to start a company, but that it would be sprung out from one of my father's research discoveries was never part of the plan." Indeed, like many father and son relationships, this one was not friction-free, and many times Kristian and Karl differed in opinion.

"I remember when Kristian was in high school and I asked him about his career plans, he told me that he did not want to work with anything that I did. Studying molecules, working like an idiot for low wages was nothing for him." Karl laughs at the memory, "Now he is my closest colleague."

"Yes, I was hesitant," Kristian says. "But I'm glad we did it. BioLamina has brought us closer together, now that we have a joint project. Karl is a professor, solidly planted in the research, and he has given me free reigns when it came to the business side."

"I started writing a business plan. It was scary. I had no experience in running a company," says Kristian. "I had an idea of what I wanted to do, to put these biologically relevant proteins that fsupport stem cell culture like no other matrix on the market, available to all researchers globally. We applied for money from the Swedish innovation agency Vinnova and we received 5 million SEK (500,000 EURO). With that grant, we could develop the protein production method. However, though the business idea was clear, the company still lacked the necessary funding."

During this time, Kristian lived in an apartment in Stockholm, neighbors with Magnus Kenneby, a management consultant at the time. They met in the shared laundry room of the apartment building and, as luck would have it, struck up a conversation.

"I had met Magnus before and knew his background, and I needed someone like him to test my ideas on. After a well-presented elevator pitch, he decided to contribute financially with money from his own pockets. He also got his family, colleagues, and friends to invest. It's much due to Magnus' support and knowledge that BioLamina was started," says Kristian.

BioLamina's first facilities at the Karolinska Institutet Science Park. Two rooms with office space and logistics in one room and lab space in the other.

"I was determined never to work with the same thing as my father. Now he is my closest colleague."

Kristian Tryggvason

"In the USA, you start Apple and other companies in a garage. In Stockholm, you let the ideas of fathers on parental leave bloom in the laundry room."

Karl Tryggvason

"The fearlessness to contact people who are interesting to talk to is one of Kristian's strengths," Karl adds.

BioLamina's first facilities were two rooms spanning 34m², located at the Karolinska Institutet Science Park. The office space and logistics was situated in one room and the lab space in the other.

"Initially we borrowed the equipment form Karl's lab, but soon we had to buy our own to meet manufacturing demands. The first labels for the vials were printed at my old workplace, borrowing their printer before we bought our own," Kristian explains. "Our Biolaminin products are unique, and the demand is high. We had booked orders on the products to Johnson & Johnson, even before the founding of BioLamina."

It was only when the pile of Styrofoam boxes in Kristian's office started to decrease that he realized that BioLamina was moving in the right direction. One year after the company was formed, BioLamina had grown to four people. One year later, in 2012, the team moved to its current site in Sundbyberg in Stockholm, with large, high quality lab and office spaces.

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"It has been such a great journey," says Kristian. "As for many small startups, there were ups and downs, and at times we have had to fight for survival. We were growing fast, and we had to make substantial investments, so it was not until 2017 that we had our first profitable year. Now we have a production standard so that some of our products can be used for cultivation of cells that are going to be used in the clinic. We have scaled up our production method to ensure that we can meet the growing demands, we have found a price range where we can be both profitable and compatible, and we have a strong base of large routine customers and many scientific publications that show the benefit of our products."

Now, after these first ten years, our small company is a somewhat important component in the stem cell culture industry," says Kristian. He continues, "We will continue to focus on our new goal, to become a leading solutions provider for cell-based therapy. I am so proud that our Biolaminins are involved in ongoing clinical trials. Even though it is early days and only a few people have been treated so far, it is in many ways a fantastic achievement. Moreover, it could not have been done without the amazing teamwork, from our side and our partners, with a lot of effort and determination. The interaction with all these extraordinary, brilliant people, that is what has made the biggest impression on me over the past ten years. That is awesome!" •

"The interaction with all these extraordinary, brilliant people, that is what has made the biggest impression on me over the past ten years."

Photo: Håkan Lindgren.

Important Events

NOV 2008
PUBLICATION IN *NATURE BIOTECHNOLOGY*

The collaboration between Professors Karl Tryggvason and Outi Hovatta resulted in this article that shows how Biolaminin 511 can be used as a substrate for culture of mouse ES cells in vitro. The cells grow as a monolayer with high stemness homogeneity, maintained self-renewal capacity and karyotypic stability during long-term culture, even without LIF. Follow up articles showed the benefits of Biolaminin 511 also for culture of human ES and iPS cells.

FEB 2009
FIRST PRODUCT ORDER; BIOLAMININ 511, 411 AND 332

We had scientists ordering our products even before BioLamina was founded.

APR 2009
VINNOVA GRANT FOUNDING THE PRODUCT DEVELOPMENT OF OUR LAMININ 511 PRODUCT

This grant was essential as it allowed us to expand our product manufacturing capacity needed for sales.

MAY 2009
CEO STARTS. OFFICIAL BIRTHDAY OF BIOLAMINA

DEC 2009
LAUNCH OF BIOLAMININ 211 LN (LN211)

FEB 2009
DISTRIBUTORS IN JAPAN AND CHINA

We were looking for distributors that sold medium which could have good synergies with our products. It has been a good collaboration and in the beginning our sales in Japan were more than a half of our total sales.

JAN 2011
MOVE TO CURRENT FACILITIES IN SUNDBYBERG IN STOCKHOLM

JUN 2011
LAUNCH OF BIOLAMININ 111 LN (LN111)

JUN 2011
LAUNCH OF BIOLAMININ 521 LN (LN521)

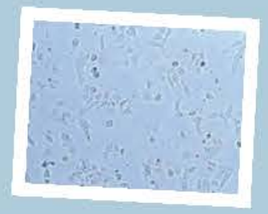
APR 2012
LAUNCH OF BIOLAMININ 421 LN (LN421)

JUN 2012
LAUNCH OF LAMSCREEN

MAR 2013
DISTRIBUTION AND R&D DEAL WITH ROCHE APPLIED SCIENCES

The technology got acknowledged by a major pharma company. This pushed us to improve our quality thinking and we got our ISO-9001 certificate.

JUN 2013
LAUNCH OF 521-TO-GO, BIOLAMININ 521 PRE-COATED PLATES



JAN 2014
PUBLICATION IN *NATURE COMMUNICATION*

A landmark paper and an important scientific validation of our Biolaminin 521 product. In September the same year, a detailed step-by-step protocol was published in Nature protocols. We had launched the product already 3 years prior, trying to sell it with our own in-house data and strong conviction, but with the scientific evidence about the superiority of the product to support reliable hESC expansion, sales increased rapidly.

SEP 2014
VINNOVA GRANT, CELL HEALTH: COLLABORATION FOR DEVELOPMENT OF BIOLAMININ 521 CELL THERAPY GRADE

This grant gave us a possibility to start the scaleup process of Biolaminin 521 CTG and to produce it in a way that is acceptable to our translational customers.

SEP 2014
VINNOVA GRANT FORSKA OCH VÄX: SUSPENSION CULTURE OF HPSCS WITH BIOLAMININ 521

JAN 2015
EU GRANT, CLINIMATRIX: FOR MARKET INSIGHT WORK AS PREPARATION FOR THE CELL THERAPY GRADE PRODUCT LAUNCH

JUN 2013
SIGNED AGREEMENT WITH CEVEC FOR SUSPENSION CULTURE PRODUCTION OF OUR CELL THERAPY GRADE BIOLAMININ 521

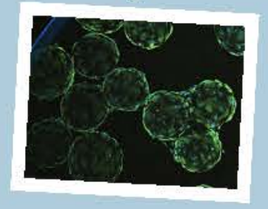
MAY 2014
ISO 9001 CERTIFIED

SEP 2014
PUBLICATION IN *NATURE PROTOCOLS*

Detailed step-by-step protocols for transfer, clonal growth and monolayer expansion of hPSCs on Biolaminin 521 under defined and animal component-free conditions.

OCT 2014
EU GRANT, LAMMIC: COLLABORATION FOR DEVELOPMENT OF CT521 COATED MICROCARRIERS

Photo: Liselotte Antonsson



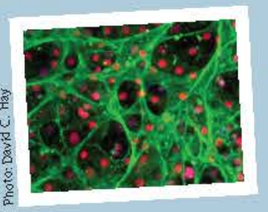


Photo: David C. Hay

APR 2015
PUBLICATION IN *BIOCHEMICAL ENGINEERING JOURNAL*

Large-scale bioreactor culture of MSCs with Biolaminin 521 coated microcarriers. Proof-of-concept article for effective serum-free expansion of MSCs.

NOV 2015
PUBLICATION IN *STEM CELL REPORTS*

hESC cultured on Biolaminin 521 and 111 show efficient hepatocyte specification, maturation, function and stabilization of phenotype. The results presented in the paper represent a significant advance compared to any previous published data especially regarding metabolic activity and functional organization.
Read more on page 82.

JAN 2016
PUBLICATION IN *STEM CELL REPORTS*

In this article, α-5 laminin is identified as a signature ECM component, endogenously synthesized by undifferentiated hESC and hiPSC cultured on defined substrates. Knockdown and disruption of the LAMA5 gene dramatically reduced hPSC self-renewal and increased apoptosis (without affecting the expression of pluripotency markers) which only culture on exogenous Biolaminin 521 could restore to wild-type levels.

MAR 2015
GLOBAL DISTRIBUTION DEALS WITH CORNING AND THERMO FISHER SCIENTIFIC

The distribution deals were a key factor to get access to the global market. It also showed the competitive edge of our products.

JUL 2015
EU GRANT: DEVELOPMENT OF BLOOD BRAIN BARRIER MODEL USING BIOLAMININS

JAN 2016
PUBLICATION IN *STEM CELL REPORTS*

This publication describes effective differentiation production of hESC-RPE cells on Biolaminin 521 in a xeno-free and defined manner. The transplanted RPE cells showed long-term integration and formed polarized monolayers exhibiting phagocytic and photoreceptor rescue capacity in a large eye model.
Read more on page 66.

FEB 2016
LAUNCH OF BIOLAMININ 221 LN (LN221)

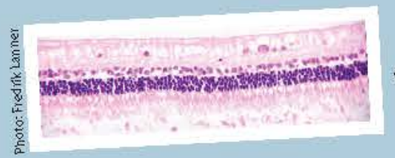


Photo: Fredrik Lanner

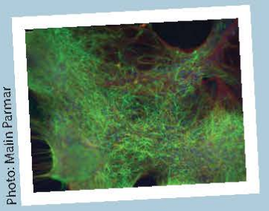


Photo: Malin Parmar

OCT 2016
LAUNCH OF
BIOLAMININ 121 LN (LN121)

JAN 2017
PUBLICATION IN *CELL STEM CELL*

This article describes a good manufacturing practice (GMP) differentiation protocol for highly efficient and reproducible production of transplantable dopamine progenitors from hESCs on Biolaminin 111. The authors also identified predictive markers expressed in dopamine neuron progenitors that correlate with graft outcome in an animal model of Parkinson's disease. Read more on page 76.

SEP 2017
PUBLICATION IN *NATURE PROTOCOLS*

A detailed 16-d protocol for obtaining high-purity ventral midbrain dopamine progenitors for intracerebral transplantation into animal models and for in vitro maturation into neurons. They show how to precisely set the balance of patterning factors to obtain specifically the caudal VM progenitors that give rise to DA-rich grafts. This protocol is free of xeno-derived products and can be performed under good manufacturing practice (GMP) conditions. Read more on page 74.

MAY 2016
GLOBAL DISTRIBUTION
DEALS SIGNED WITH
STEMCELL

DEC 2016
EU GRANT, DOPALAM:
DOPAMINE CELL PRODUCTION
USING BIOLAMININ 521 AND
BIOLAMININ 111

This grant allowed us to start the development of Biolaminin 111 CTG for dopamine cell production.

JAN 2017
VINNOVA GRANT, LTNES:
SETTING UP AN IPSC BANK
PRODUCTION OF MCB NES
WITH USE OF BIOLAMININ 521
AND BIOLAMININ 111

MAY 2018
LAUNCH OF
BIOLAMININ 521 MX (MX521)
AND BIOLAMININ 521 CTG (CT521)

Launch of our cell therapy grade Biolaminin 521 product. At the same time, we changed the name of all our human recombinant laminin products to Biolaminin.

MAY 2018
PARTNERSHIP WITH NOVO NORDISK
(LICENSING DEAL)

Partnership between Novo Nordisk, BioLamina and Lund University to develop stem cell-based treatments for Parkinson's disease. Another partnership between Novo Nordisk, Biolamina and DUKE National University Singapore Medical School for research was started with focus on chronic heart failure and age-related macular degeneration.

MAY 2018
PUBLICATION IN
BIOMATERIALS

This article shows laser-assisted bioprinting production of 3D cornea tissues using human stem cells and Biolaminin 521 functionalized bioink. Read more on page 56.

Photo: Karl Tryggvason

SEP 2018
PUBLICATION IN *MATRIX BIOLOGY*

Article showing a novel method to grow and maintain normoxic and functional islets on Biolaminin 521 in a serum-free medium.

AUG 2018
OEM DEAL WITH CELLINK

OEM partnership with CELLINK for the development of bioink products for bioprinting. CELLINK launched a portfolio of LAMININK with Biolaminin 111, 121, 411 or 521 incorporated.

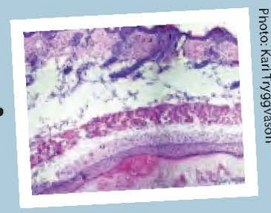


Photo: Karl Tryggvason

OCT 2018
PUBLICATION IN *NATURE COMMUNICATIONS*

Article where Biolaminin 511 and 421 were identified as potential candidates to replace the murine feeders for robust expansion of adult human skin keratinocytes.

OCT 2018
VINNOVA GRANT, LAMINK:
FOR NK CELL DIFFERENTIATION
ON BIOLAMININ

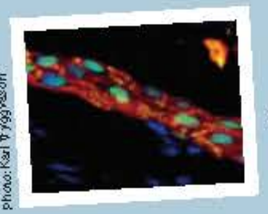


photo: Karl Tryggvason

JAN 2019
PUBLICATION IN *STEM CELLS INTERNATIONAL*

Large-scale hiPSC culture in hollow fiber bioreactors coated with Biolaminin 521 show significant increase in proliferation.

MAR 2019
PUBLICATION IN *CELL REPORTS*

Protocol for reproducible generation of clinical-quality, stem cell-derived cardiovascular progenitors on Biolaminin 221.

MAR 2019
EU GRANT, RESTORE: BIOLAMINA SUPPORTS THIS FLAGSHIP PAN-EUROPEAN PROGRAM, DESIGNED TO ACCELERATE THE CLINICAL AVAILABILITY OF ADVANCED, REGENERATIVE MEDICINE.

MAR 2019
OEM DEAL WITH SPIBER

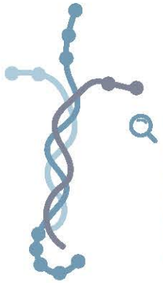
OEM partnership with Spiber to develop a laminin-based, bio-specific 3D-culture matrix.

MAY 2019
SUSPENSION PRODUCTION IMPLEMENTED IN HOUSE

JUNE 2019
LAUNCH OF BIOSILK 521

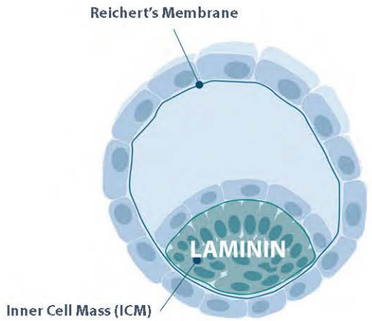
Laminin-based 3D-culture matrix

"We are fortunate to work with some of the best researchers and industry professionals in the world, and we are thrilled to see how our products are being used to move their innovations forward. We look forward to continuing this journey together."



THE LAMININ MOLECULE

Laminins are heterotrimeric proteins that contain an α-chain, a β-chain, and a γ-chain. The laminin isoforms are named according to their chain composition.



LAMININ EXPRESION IN THE BLASTOCYST

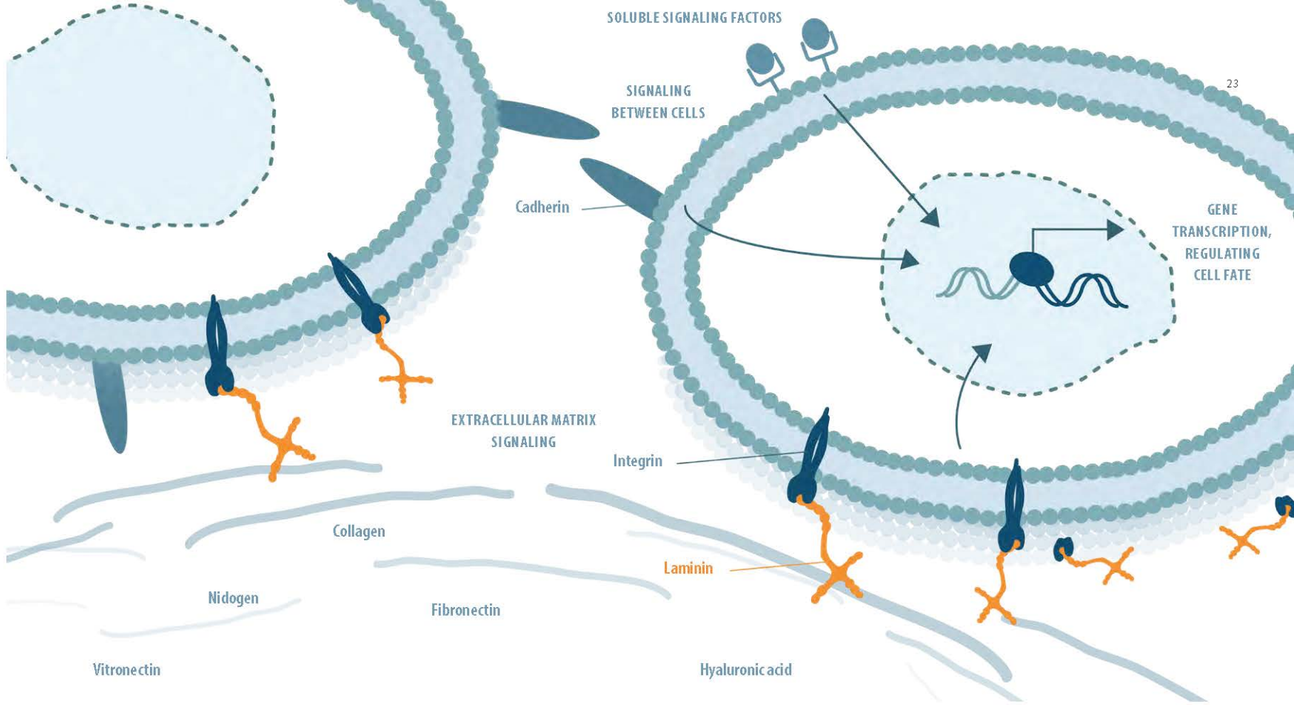
α5 chain laminins are among the first matrix proteins to be expressed in the inner cell mass of the blastocyst and are vital components of the embryonic stem cells niche.

The Laminin Technology

Laminins are a large family (at least 16 different isoforms expressed in mammals) of conserved, multidomain glycoproteins comprising the extracellular matrix. They are a major component of the basal lamina, a protein network that is the foundation for most cells and tissues. Laminins are vital for the maintenance and survival of tissues and, importantly, most laminins exhibit high cell-type specificity. Each laminin isoform consists of three inter-coiled chains - an α, β, and γ chain – that exist in five, four, and three genetically distinct variants, respectively. The laminin isoforms are named according to their chain composition. For example, a combination of an α5 chain, a β2 chain, and a γ1 chain, forms laminin 5-2-1 (LN521). The trimeric proteins form a cross-like structure that can bind to other extracellular matrix molecules and various cell membrane receptors.

There are many binding motifs on the full-length laminin molecule that can interact with cell membrane receptors, both in the short arms and in the long arm. Via binding to specific cellular receptors, such as integrins and dystroglycans, laminins mediate cellular effects including, but not limited to, cell adhesion and survival, proliferation and migration, differentiation and specialization, and subcellular organization. Without the right combination of laminin isoforms, cells and tissues become dysfunctional. Laminins are also capable of co-signaling with growth factors and efficiently buffer endogenously produced growth factors, thereby adding to the mechanistic complexity.

In the body, cells reside in highly specialized, chemo- and mechanosensitive microenvironments, or "niches", which serve to protect and maintain the cells and to respond to the needs of the surrounding tissue. α5 chain laminins (511 and 521) are the key cell adhesion proteins of the natural stem cell niche, expressed and secreted by the embryonic stem cells of the embryo's inner cell mass. The Biolaminin 521 cell culture substrate thus recapitulates the most biologically relevant milieu for hESCs and iPSCs cultured *in vitro* and is a critical autocrine and paracrine factor for regulating survival and self-renewal. Tissue specific laminin isoforms can also be used for robust differentiation of specialized cell types, such as hepatocytes, skeletal muscle cells and various neural cells. •



THE EXTRACELLULAR MICROINVIRONMENT

Stem cells are influenced by the coordinated interaction of soluble factors, extracellular matrix (ECM) proteins, and signals from neighboring cells. This multifaceted cell-ECM communication takes place through both integrin and non-integrin membrane-bound receptors and induces complex intracellular signaling pathways with subsequent effects on survival, self-renewal, migration, morphogenesis, and differentiation.

BASEMENT MEMBRANES

The basement membranes (BMs) are sheet-like extracellular matrix (ECM) structures that are located in the immediate vicinity of most cells, a foundation for most cells and organs. The ***basal lamina*** is a layer of the basement membrane and is made and maintained by the cells that sit on it. It acts as a point of attachment for cells, achieved by cell-matrix adhesions.