

COLLAGEN GENE



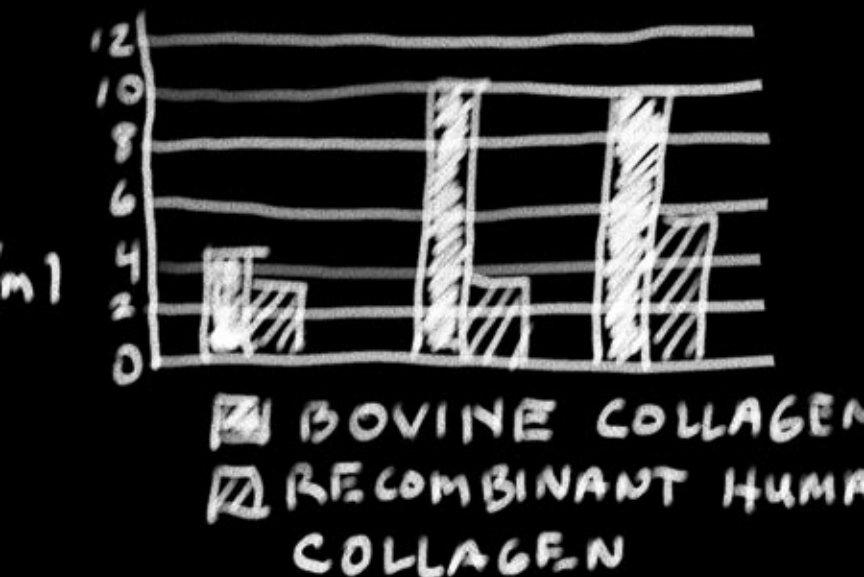
UNSTABLE + PROLY
HYDROXYLASE



HYDROXYLATED
STABLE TRIPLE
HELICAL COL

COMBINANT HUMAN COLLAGEN

FULLY SYNTHETIC
HUMAN SEQUENCE PROTEIN
SAFE
PURE
MODIFIABLE



FibroGen Europe, Ltd.

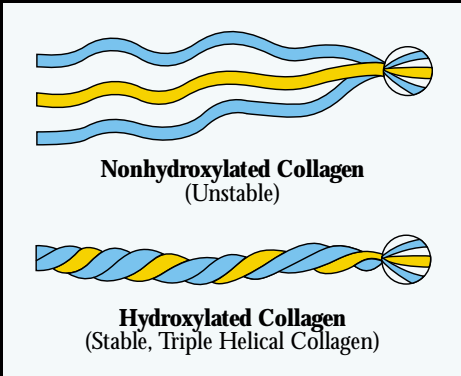
Headquartered in Helsinki, Finland, FibroGen Europe is a biotechnology company focused on the development and commercialization of recombinant collagens and gelatins.

The Company's expertise in extracellular matrix technology coupled with its substantial intellectual property position allows FibroGen Europe to assume a leadership position in the recombinant collagen and gelatin marketplaces.

FibroGen Europe will focus its efforts on supplying its novel biomaterials to companies in the medical device and pharmaceutical industries, as well as commercializing products of its own design.

FibroGen Europe is a subsidiary of FibroGen, Inc., San Francisco, California.

Recombinant Collagen/Gelatin



COLLAGEN
GENE



UNSTABLE + PROLYL
HYDROXYLASE



HYDROXYLATED
STABLE

TRIPLE
HELICAL

STRATEGY

- Focus on making and supplying human proteins synthetically to replace animal derived protein for medical purposes
- Develop final product formulations for recombinant collagens in the key markets of tissue sealants and injectable applications
- Commercialize biosynthetic human gelatin for vaccines
- Supply biosynthetic animal gelatins for capsules and softgels
- Provide recombinant human collagens for research and laboratory uses

Recombinant Human Collagen

Applications

Medical devices, drug delivery, diagnostics, research reagents, tissue engineering

Technology Addressing Unmet Needs

Animal-derived collagen and its derivative, gelatin, are widely used in medical, pharmaceutical and consumer products. However, recent concerns regarding the continued use of such materials due to adverse immunologic and inflammatory responses and the potential for contamination of bovine collagen and gelatin with the agent that causes the fatal bovine spongiform encephalopathy (BSE) and its human variant, Creutzfeldt-Jakob Disease, have caused manufacturers to search for alternative materials.

Bovine collagen is used today in a large number of implanted and injected medical products. A percentage of patients develop adverse clinical problems such as prolonged redness, swelling, itching, firmness at the site of injection and hypersensitivity. In fact, inflammation is a natural but undesirable consequence to the introduction of foreign substances such as animal products into the human body.

In response to these concerns, manufacturers, consumers and regulators have been actively seeking alternatives to animal collagens. FibroGen is addressing this need through the development of its recombinant human collagens.

MANY BIOMEDICAL USES OF COLLAGEN

- Hemostats
- Tissue sealants
- Artificial skin
- Artificial dura
- Drug delivery
- Gene vector stabilization
- Stem cell expansion
- Implant coatings
- Corneal shields
- Wound dressings
- Tissue engineering
- Engineered prosthetic devices
- Cell preservation
- Wrinkle and scar treatments
- Incontinence treatments
- Bone graft substitutes
- Antiadhesion barriers
- Research reagents

Recombinant human collagens are human proteins providing the potential benefits of eliminating immune reactions or transfer of pathogens from animal material. Aside from the potential safety advantages of human collagen, FibroGen's technology offers the opportunity for manufacturers to choose the appropriate collagen type for their desired application. Additionally, using techniques such as removing cleavage sites and adding binding sites offers the possibility of creating "designer" collagens to optimize specific properties.

There are 20 different types of collagen, each with specific roles in the body including, for example:

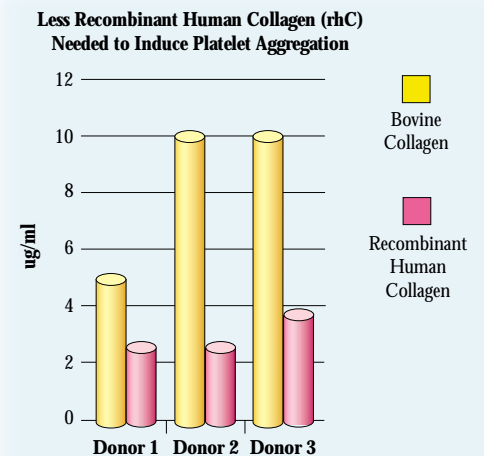
- Bone, Skin—Type I
- Cartilage—Types II, IX, XI
- Vascular/Hemostasis—Type III
- Basement Membranes—Type IV
- Angiogenesis Control—Type XVIII

FibroGen scientists have successfully expressed nine of these collagens, with early development efforts focused on type III for hemostats and tissue sealants, type I for bone and dermal repair, and type II for cartilage applications.

FibroGen has a strong proprietary position on recombinant human collagen, including the *multi-gene recombinant expression method*, compositions, pharmaceutical and therapeutic molecules, and commercial applications. FibroGen's *multi-gene* process is the only known commercially viable method of making thermally stable, recombinant human collagen.

"Our goal was to take these ubiquitous essential building blocks and re-create them into useful and safe biomaterials for applications both known and not yet known."

Kari I. Kivirikko, M.D., Ph.D.
Professor, Finland Academy of Sciences, Scientific Cofounder, FibroGen, Inc.



In an ex vivo analysis of platelet aggregation using blood from three healthy volunteers, less collagen is required to cause complete aggregation when recombinant human collagen is used.

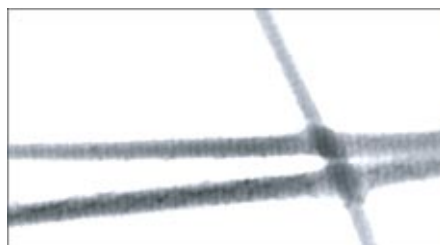
ADVANTAGES OF RECOMBINANT HUMAN COLLAGEN

- Fully synthetic (simple carbon source plus salt media)
- Human sequence protein (produces no immunologic reaction)
- Safe (no transfer of pathogens)
- Pure (specific types for specific applications)
- Modifiable (ability to engineer)

FibroGen's proprietary *multi-gene* method involves the coordinated expression of genes encoding collagen and those encoding necessary enzymes to produce triple-helical, recombinant, human-sequence collagen, which is stable at biologically relevant temperatures. This characteristic makes the materials uniquely suited for biomedical applications such as tissue sealants, dermal injections to correct scars and wrinkles, implant coatings and wound dressings.

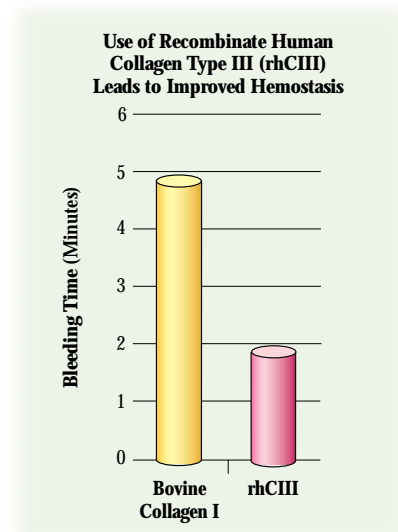
FibroGen uses a unique set of technologies to produce specific types of pure, reproducible and quantifiable recombinant collagens and gelatins. FibroGen's proprietary *multi-gene* method allows the production of collagen and gelatin in systems that do not normally produce collagen, including yeast and plants. Although FibroGen anticipates that initial commercial production will be in yeast, the company is concurrently developing other production systems. FibroGen has proven that it can produce collagen in transgenic plants and animals. The Company is pursuing transgenic plant production to meet the demand for high-volume, low-cost collagens and gelatins for specific applications.

The manufacturing process in yeast is already in place, and FibroGen is scaling up its fermentation production in collaboration with a contract manufacturer. Commercial scale quantities of FibroGen's synthetic collagens are expected to be available in early 2001.



FibroGen's Recombinant Human Collagen Type I Fibrils

Note the banding pattern characteristic of authentic collagen.



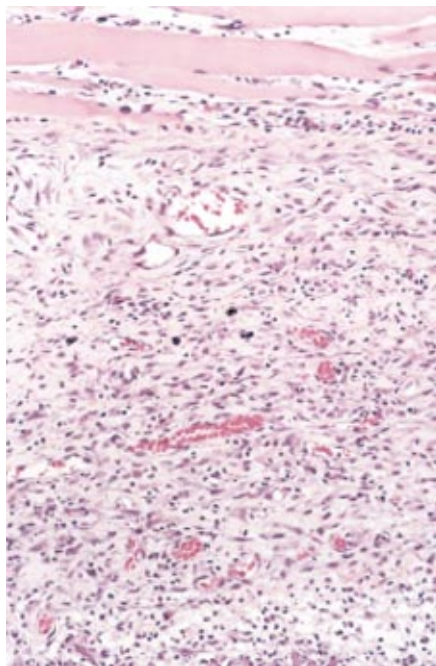
In vivo analysis of hemostatic sponge formulated with recombinant human collagen type III as compared to one made from bovine collagen demonstrates a significant reduction in the time required to halt bleeding with recombinant human collagen type III.



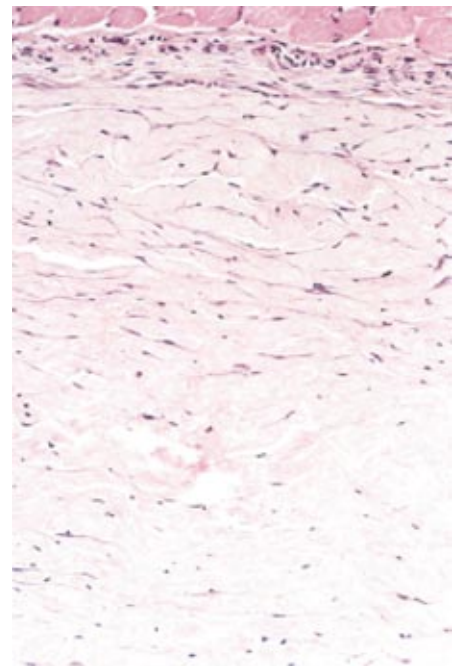
FibroGen's collagen development team includes scientists at the Company's South San Francisco facility and at its subsidiary, FibroGen Europe, in Helsinki, Finland. Collectively, they are working with companies to incorporate FibroGen's recombinant human collagen into numerous medical devices, diagnostics and new-product concepts. Initial efforts have focused on production of recombinant human collagen types I, II and III, and samples have been provided to potential partners for evaluation and testing. In addition to the many benefits of recombinant human collagen materials, FibroGen's strong patent position offers the advantage of prolonged differentiation to our collaborators' products.

Combining the overall properties of collagen as a structurally strong and reliable biomaterial with the advantages gained through the use of human collagen rather than animal-derived collagen, FibroGen's recombinant human collagen technology presents a unique opportunity to develop superior and truly biocompatible medical products.

Tissue Response of Collagen-Based Hemostat in Rat Subcutaneous Model



Commercial Product



Recombinant Human Collagen Type III

Comparison of the response to a subcutaneously implanted, commercially available collagen hemostat (L) and a recombinant human collagen type III hemostat (R) demonstrates increased biocompatibility and significantly reduced inflammation and tissue response with recombinant human collagen type III.

Biosynthetic Gelatins

GELATIN IS A COMMON BIOMATERIAL

- Vaccine and drug stabilizer
- Hard and soft gelatin capsules
- Infusion solutions
- Tablet binding agent
- Cell storage and preservation

CONCERNS

- Potential for contamination with pathogens
- No viable alternatives

SOLUTION

- Biosynthetic gelatins

Applications

Pharmaceutical, medical, laboratory and fine chemical applications

Technology Addressing Unmet Needs

Gelatin is a critical component in many products of the pharmaceutical, research, photographic, high technology, cosmetics, and food and beverage industries. In the pharmaceutical industry, for example, gelatin is used in vaccine stabilizers, coatings for hard and soft gelatin capsules, infusion solutions and binding agents in tablets.

Gelatin historically has been produced from animal tissue discards after rendering. Some of these tissues include bovine brain, spinal cord and bone marrow. Recently, these tissues were classified by the European Commission as “specified risk materials” due to the high concentration of BSE infection and have been the subject of proposed

bans in medical products. With current production methods, it is difficult to control and ensure the safety of the animal parts used to make animal-source gelatin. Concerns over the potential contamination risk associated with these production methods are compounded by the huge volume of bovine materials used in pharmaceutical products and a lack of viable replacements to animal-derived gelatin.

Animal-derived gelatin also is used as a stabilizer in live-virus vaccines and several approved drugs. Immune reactions to some of these vaccines have been reported.

Although alternatives have been identified in a few applications, for most gelatin-based processes and products the performance characteristics of this key material have not been duplicated and substitutes not adopted. In light of these

concerns, considerable demand has been created for gelatin replacement products.

FibroGen is responding to this need by developing the first recombinant gelatin product—a downstream product of FibroGen’s recombinant collagen production technology.





FibroGen's proprietary *multi-gene* technology enables the production of gelatin precursor collagen through the use of highly efficient recombinant expression systems such as recombinant yeast fermentation and transgenic plant expression. While FibroGen's recombinant gelatin technologies can be applied across the entire spectrum of the current gelatin market, the Company's initial focus will be on the pharmaceutical and other high technology markets.

FibroGen's proprietary recombinant collagen technology enables the production of gelatin in a synthetic and reproducible manner lending itself as a rational substitute with the desired performance characteristics. These characteristics include cGMP manufacturing, quality, consistency and no potential contaminants.

FibroGen's technology can be used to make biosynthetic human gelatin for such applications as vaccines and drugs *or* biosynthetic animal gelatin for hard and soft gelatin capsules.

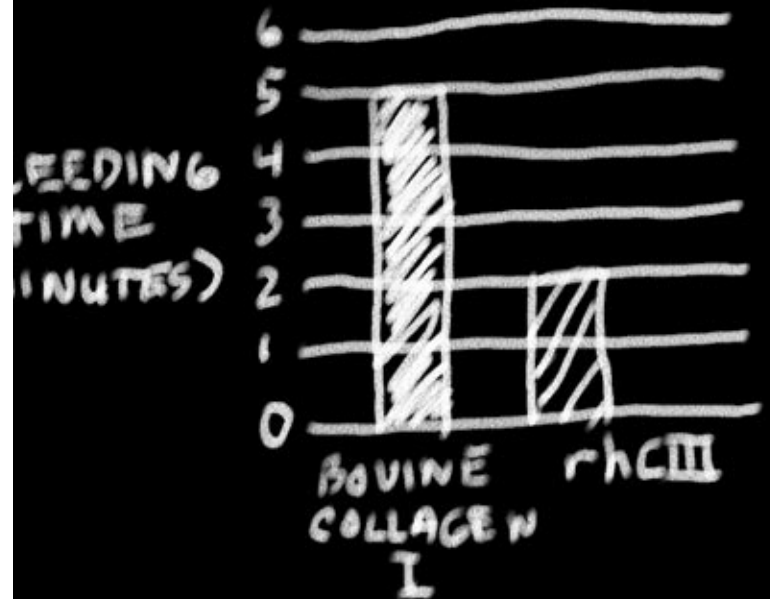
ADVANTAGES OF BIOSYNTHETIC GELATIN

- Available as human gelatin or animal gelatin
- A "natural" product, synthetically produced
- Free of pathogens
- Consistent lot-to-lot
- Compatible with current manufacturing processes
- Simplifies record keeping
- Reduces manufacturing process costs
- Allows product differentiation
- Promotes market expansion

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MEDICAL USES OF COLLAGEN

- HEMOSTATS
- ISSUE SEALANTS
- ARTIFICIAL SKIN
- ARTIFICIAL DURA
- DRUG DELIVERY
- GENE VECTOR STABILIZATION
- STEM CELL EXPANSION
- IMPLANT COATINGS
- CORNEAL SHIELDS
- WOUND DRESSINGS
- ISSUE ENGINEERING
- ENGINEERED PROSTHETIC DEVICE
- CELL PRESERVATION
- WRINKLE AND SCAR TREATMENTS