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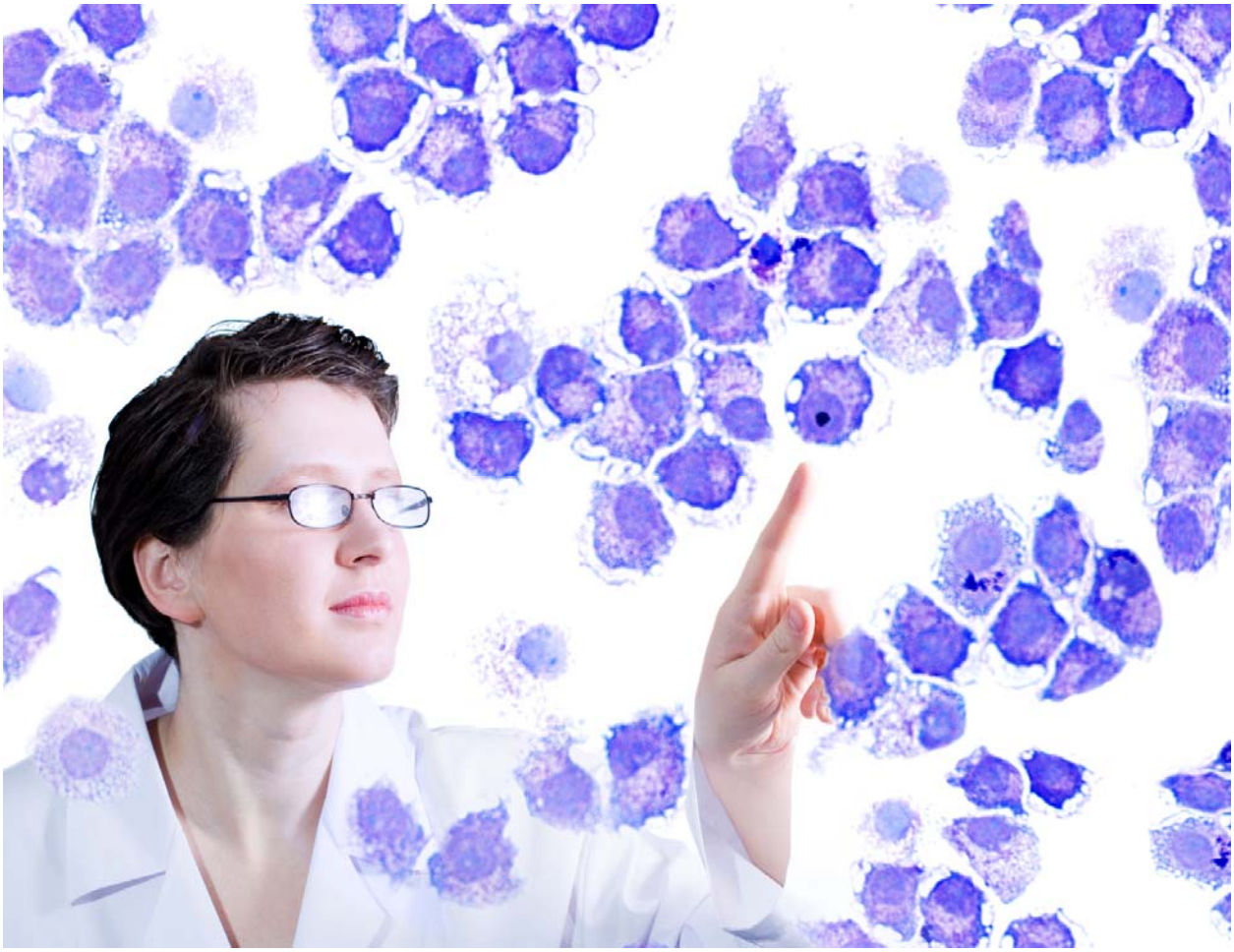
Tissue Engineering With Biopolymers

Tracheal epithelial cells have never been successfully replaced or replenished, owing to their "non-re-epithelializable" nature. Once lost through chemical (drug) action, intubations or other means, there is currently no natural or artificial way to regroup these cells on the inner wall of the trachea. A team of University at Buffalo researchers has come up with an integrated set of technologies enabling the study, research and treatment in the area of cell and tissue reconstruction and drug delivery mechanisms. From the initial research on tracheal lumen, this team has identified methods and processes to synthesize, study kinetic reactions, and control protein discharge of biodegradable polymers for any other tissue reconstruction system. This technology potentially enables one to re-epithelialize the tracheal lumen, an unachievable feat till date.



Tissue Engineering With Biopolymers

OVERVIEW

Tracheal epithelial cells have never been successfully replaced or replenished, owing to their "non-re-epithelializable" nature. Once lost through chemical (drug) action, intubations or other means, there is currently no natural or artificial way to regrow these cells on the inner wall of the trachea.

There exists tremendous need in health related markets for methods and compounds that enable study, analysis and treatment of tracheal (and other) epithelial cell loss or damage. Such methods have wide applications, real and potential, in numerous areas wherein methods of healing and treatment do not exist.

The possession of an in vitro cell culture model of the tracheal lumen, and also of degradable biomaterials capable of timed release proteins, are imperative musts in researching treatment procedures in the following areas:

- Re-epithelialization in human and animal body segments
- Research in cell culture, inter-cellular interaction and protein release and delivery
- Tissue scaffoldings and wound healing situations
- Drug delivery and release mechanisms

INVENTION

These inventions offer comprehensive value in the areas of **tissue engineering** and **drug delivery** systems, encompassing the following set of value propositions:

An in vitro synthesized model of the tracheal lumen. – for use in understanding the underlying structure and functionalities of this body part so that medical treatment, prophylactic or cure, can be better administered

Novel method to study reaction kinetics of biodegradable polymers – has important applications in creating implantable surfaces within the human body. Organic cells can be cultured on controllably degradable bases and integrated onto tissues within the body

Synthesis and processing of specific kinds of biodegradable polymers – since fine-tuning and specialized requirements are important for most applications

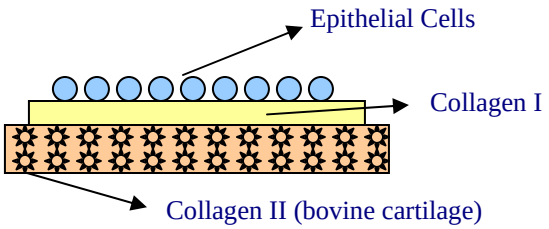
Controlled protein discharge from biodegradable surfaces – has significant applications where cells cultivated in vitro have to be implanted and organically integrated with natural tissues in specific body parts

These can also be used in scenarios requiring efficient and controlled drug delivery to specific regions in the human body.

I: Tracheal Lumen model

Tracheal epithelial cells have been grown on an organic substrate fed with required nutrients. The resulting model can be used as a research tool, as well as a source of implantable tissue in treatment situations.

Chondrocytes from bovine articulator cartilage were first isolated and cultured till they formed an opaque layer of extracellular matrix (type II C*ollagen*), providing the necessary *connective* tissue necessary for growth of epithelial cells. Since Respiratory Epithelial Cells (RECs) will not grow on *Collagen II*, a layer of *Collagen I* is spread over the chondrocyte layer. The RECs are then plated on to this layer.



The results are similar to those seen in *in vivo* studies, viz., incomplete and/or slow re-epithelialization. This enables research on re-epithelialization and the impact of drugs or chemicals on such re-epithelialized tissue.

Benefits

Cells grow in a manner similar to *in vivo* re-epithelialization in the tracheal lumen (in discrete patches but not unto confluence).
Precise set of compounds and factors controlling cell growth and organic interactivity with surroundings has

Possible offshoot research includes re-epithelialization and over-epithelialization problems, and interactivity between epithelial and connective tissue.

Examples of applications

(a) The technology has the potential to be a novel method of tissue engineering by replacing damaged tissue through implantation into humans and animals
(b) The roles of compounds such as *transforming growth factors (TGF)* and *cytokines* in re-epithelialization can now be tested *in vitro*
(c) Fistulas implanted in dialysis patients become over-epithelialized and blocked. This system can provide insight into methods or drugs preventing this situation.
(d) This model aids investigation of interactions between chondrocytes and epithelial cells, looking at (whether factors secreted by one inhibits or stimulates growth of the other).

II: Reaction bio-kinetics study

Background

In vivo and *in vitro* techniques are used to study hydrolytic biodegradability of polymers. Although *in vitro* is the major clinical study method, direct monitoring of polymer implant weight losses and histological observations (that provide macroscopic information on the degradation) are time-consuming.

In vitro techniques such as Scanning Electron Microscopy (SEM) and Static Secondary Ion Mass Spectroscopy (SSIMS) are mostly surface sensitive microscopic and spectroscopic procedures. These do not provide details of chemical composition or structural information, and study one or a combination of polymer factors (molecular weight, tensile strength, thermal properties, hydrolysis, etc.) at the initial and final phases of the biodegradation process. Nothing is known about the many sub-stages in-between, and no control can be exercised on the progress of the reaction.

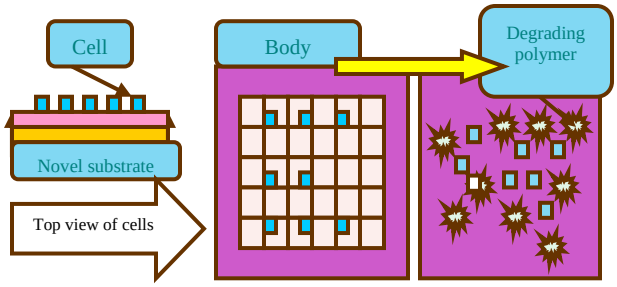
This technology incorporates SIMS, XPS and dynamic study techniques in Time of Flight (ToF) studies of degradation of Polyglycolic acid (PGA). *Hydrolytic degradation products* of PGA can be directly observed in the ToF spectra in the form of intact molecular ions. This is found to be a general phenomenon for different classes of biodegradable polymers.

Results and Benefits

Study of reaction (degradation) products on the surfaces of materials possible in high mass range up to *10000 atomic mass unit* (amu)
Study the reaction rates and kinetics at different stages of a process, from start to finish
Study of molecular weight distribution of degradation products using statistical averaging methods; possible in the range of *hours*
Detect and measure the above factors, achieving some form of control over degradation reactions of polymers

III: Synthesis of unique biodegradable polymers

Biodegradable polymers require specific properties and features depending on the segment of use. The inventors use Secondary Ion Mass Spectroscopy (SIMS) and other techniques to arrive at a set of polymer materials possessing unique properties.



Inventions II and III

In this invention, *fluorocarbon chains* of various lengths of *carbons (3,7,10)* have been synthesized as terminal end groups of *polyglycolic acids, polylactic acids* and *poly (lactic-co-glycolic) acid* polymers. **Also**, polymer chains with 1,2 and 4 fluorocarbon were synthesized using *ring opening polymerization* methods as well as methods of *insertion/ substitution* of the fluorocarbon at a terminal hydroxyl group. **Additionally**, various preparation methods that produce surface segregation of fluorocarbon chains that dominate the entire surface and create a material with a fluorocarbon overlayer were designed.

Benefits

Design of surface chemistry for biologically specific adhesion **enabling** better organic integration in medical applications

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Better degradation kinetics enabling better control over formulation.
Potential to extend and improve technology through combinations with other materials

The above inventions provide a platform to achieve implantation of in vitro cells into the body and control drug delivery. Study of specific proteins, reaction kinetics and controlling factors are required for the integration of foreign cells into the native ones.

IV: Protein delivery kinetics (from Biodegradable)

This invention provides complementary techniques to the above set of inventions. In order to facilitate implantation and ***organic integration of epithelial cells*** within the human body (e.g. tracheal lumen), the precise nature and delivery kinetics (amounts, timings, excitation states, etc.) of ***proteins*** needs to be understood and controlled. This invention deals with

Whether protein structures and functions change if placed within specific biopolymers
Requirements for holding and releasing proteins from within specified biopolymer based matrices at specific times and levels
Concentrations at which *bioactive* proteins are released from polymer matrices (bioactive proteins form subsets within proteins)
Overriding protocols required to stabilize and release proteins from biopolymers as above

Results and benefits

This invention creates a ***two-layer*** biopolymer based architecture and allows for release of ***two proteins*** from the same. The releases are done in a ***choreographed*** manner at specific instants and of the appropriate amounts.

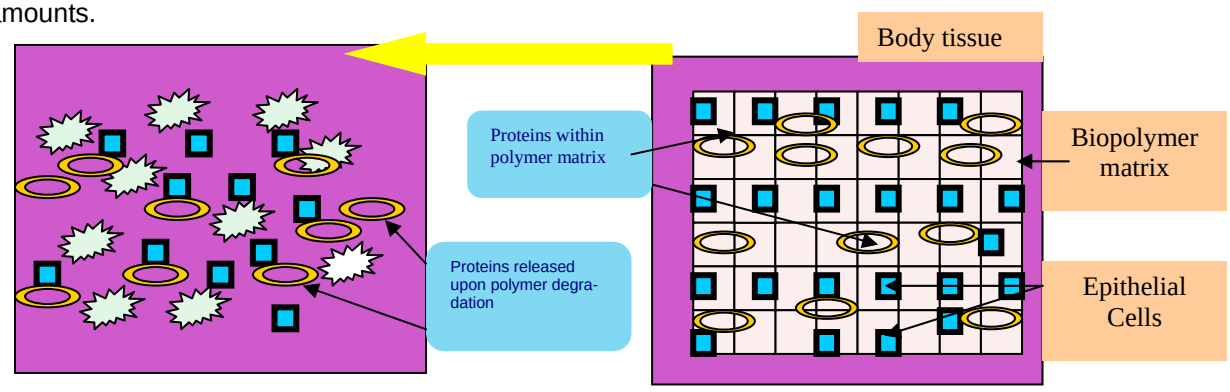
Keratinocyte growth factor (KGF) and *Transforming Growth Factor alpha* (TGF-a) proteins were both used and successfully released.

Biopolymers and solvents were employed in various embodiments and combinations to get the best results. *Lead* was added since the polymer blends formed thereupon were seen to release KGF and TGF in manners similar to natural processes. Based on studies undertaken of these protein releases, several viable lead based polymer blends were developed.

The protein release kinetics can be varied by two orders of magnitude. Varying the molecular weights of polymers enables control over the release kinetics. Also, pin printed analyte detection technology was used to screen more than two polymers at a time to get the best blends.

V: Restorable Laminated Repair Membrane for accelerated and sustained wound repair

The invention describes a multi-layered structure wherein biodegradable polymer layers embedded with curative proteins are placed on top of another polymer layer that acts as a barrier. The barrier acts to prevent in-growth of other cells onto the injured area as well as stops re-epitheliazation-impeding enzymes from hindering the process. The protein-embedded layers are designed to release proteins in active form in a choreographed manner so that the natural conditions that help establish epithelial growth are formed. This means that given a specific type of injury in a specific region, the required proteins can be released in desired quantities at desired times to stimulate epithelial formation.



Invention IV

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MARKETS

Tissue Engineering Market à about $ 10 billions in the US currently growing at around 8%. This is again a subset of the total wound healing market in the US which includes markets that do not require any tissue engineering. Of the above tracheal epithelialization healing market is a small segment since a large segment is devoted to bone and muscular tissue engineering. We can estimate this at less than 5%, that is a total market of about **$ 5 millions** (although tracheal cancers are among the leading causes of mortality in the US, they are not necessarily re-epithelialization cases).

Tracheal Injuries

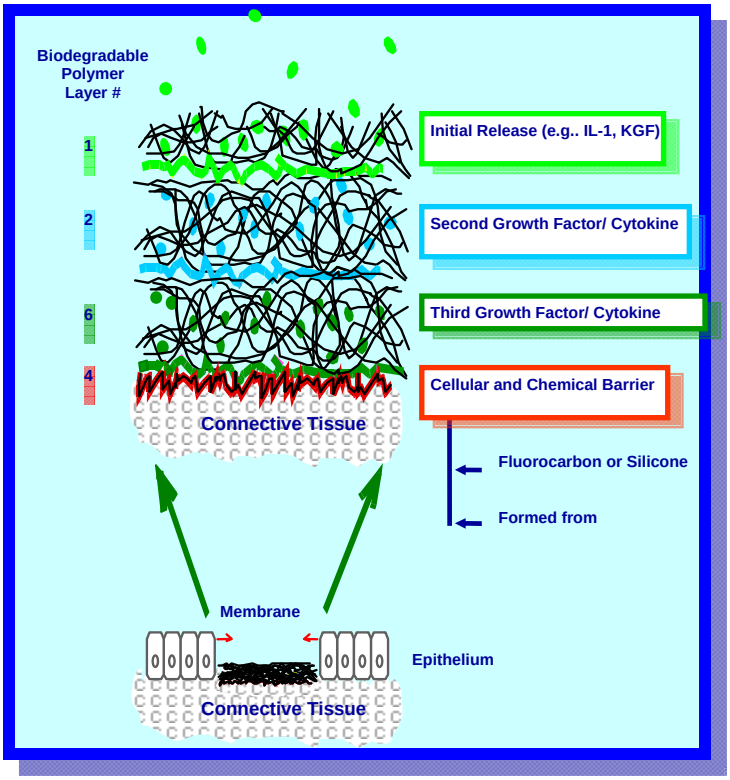
Tracheobronchial injury occurs in 0.4-1.5% of major blunt trauma patients and is found in 2.8-5.4% of trauma-related autopsies. Tracheobronchial tear also has been reported in 18% of autopsies after emergency intubation; however, since minor injuries often are not identified, the actual frequency of tracheobronchial tear may remain unknown.

Working from a data base statistic of 25310 pediatric blunt trauma cases (that accounts for almost 80% of tracheal epithelial loss), we assume that 200000 cases exist totally in the US. This means that around 1% of cases suffer from tracheal injuries which means around 2000 cases. Taking average costs to be about $ 5000 per patient, we have total costs around $ 10 millions per annum of which **$ 5 millions** will be towards tracheal epithelialization

PATENT STATUS

US Patent #6,312,952 issued for Invention I on 11/06/01 and # 6,329,4570 for Invention III on 11/06/01.

US Provisional patent #60/351,592 and #60/378,709 has been filed for Invention II and Invention IV respectively.



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