

20.441J Fall 2009

Quiz 3 Sample problem, as solved in class

Synthetic pathways for a new conjunctiva (Yannas).

The conjunctiva covers the exposed part of the opaque part of the eye (sclera) and the inner surface of the eyelids. It is made up three tissue types. The epithelial tissue is stratified and contains specialized cells (goblet cells) that synthesize and secrete mucus that contributes to the protective and lubricating layer on the exposed surface of the eye. Underneath the epithelial tissue is a very thin basement membrane and connected to it is the conjunctival stroma, a loose vascular supportive tissue comprising extracellular matrix proteins and blood vessels. See Fig. 1.

Wounds in the conjunctiva can be induced by chronic infection (trachoma) that remains untreated (typically due to unavailability of medical care in certain developing economies). Such chronic wounds can be deep, extending into the stroma and eventually closing by contraction and scar formation, processes which block vision. Typically, one eye only is compromised by this condition; however, both eyes may eventually also get involved..

You are working as a consultant in a medical device company that is interested in designing a device to be used in inducing regeneration of the diseased conjunctiva. The device that you will design will be placed in contact with a surgically induced full-thickness square wound, initially measuring 2 x 2 mm² in area, in the diseased conjunctiva. A successful device will induce regeneration of all three tissues of the conjunctiva, with recovery of function in less than 8 weeks.

In your design consideration you will make the assumption that only one eye has been affected at the time of treatment. Also assume that the conjunctiva has a morphology that is very similar (though not identical) to that of the skin of a rodent. You will also assume that the full-thickness conjunctival wound responds to regenerative treatment by a successfully selected device as if it were a full-thickness wound in the skin of a rodent. Obviously, approximating the conjunctival wound with a skin wound is a first-order approximation that only serves as a screening tool, of help in selecting a basic design strategy from among several strategies that have no chance of providing a useful answer.

Listed below are various suggestions for potentially regenerative devices that have been made to you by coworkers or suppliers of medical reagents or devices. For each suggestion, please provide either a positive or negative response and provide a brief explanation for your selection. A negative response implies that the suggestion has practically no chance of leading to a regenerated conjunctiva (little or no efficacy) or that the suggestion comes with an unacceptably high cost to the patient (little or no safety). A positive response does not guarantee success; however, it suggests that the selection has the potential of eventually providing a useful device provided other requirements are included in a future design (high efficacy) and that it is generally safe (high safety).

Your brief response for each selection should address both the efficacy and safety issues.

Perfect efficacy implies regeneration of all three conjunctival tissue types. If unsure about the safety of a substance or device, you must conclude that the safety is not high and must be specifically tested for.

A. An autologous cell culture comprising mature cells from the epithelial tissue layer of the conjunctiva from the uninfected eye will be drizzled onto the surgically wounded conjunctiva at the rate of about 2 million cells per day for a period of 14 days.

B. A porous copolymer of lactic acid/glycolic acid, comonomer ratio 75/25, that degrades with a half-life of 14 days, average pore size 100 μm , with randomly oriented pore channels is grafted on the wound.

C. A porous scaffold identical to that described in B above except seeded with 3 million epithelial conjunctival cells, identical to cells described in A above, is grafted on the wound. The cells have been seeded into the scaffold prior to grafting of the scaffold on the wound.

D. Continuous infusion into the wound over 14 days of a low-molecular weight substance X that blocks the intracellular pathway responsible for synthesis of alpha smooth muscle actin by fibroblasts. Substance X has been studied in vitro; no in vivo studies of X have been made.

E. A porous collagen/GAG scaffold, degrading with a half-life of 12 days, average pore diameter 100 μm , pore channels randomly oriented. No cells have been seeded into the scaffold prior to grafting on the wound.

Solutions.

A. This approach is expected to have no efficacy since epithelial cells by themselves are known not to synthesize the stroma in skin wounds. Its safety can be high by making sure that the autologous epithelial cells are extracted from the surgically removed conjunctival tissues that were procured when the wound in the dysfunctional eye was surgically generated. However, the design would have very low safety if it calls for extraction of cells from a biopsy of healthy conjunctival tissue from the patient's healthy eye (since it will threaten loss of normal vision in the remaining healthy eye).

B. The synthetic polymer has no efficacy because it lacks ligands for binding integrins of contractile fibroblasts. Even if there is nonspecific binding on the synthetic polymer surface, absent specific ligands there is little expectation that contraction blocking (a requirement for regeneration) will occur. The safety of the device is questionable: Even though it will eventually degrade in 2-3 weeks, the product of degradation of each of the comonomers is a pH-lowering substance (e.g., lactic acid) that should cause a local inflammatory response.

C. This system suffers from lack of specific ligands, as in section B above, and cannot block contraction. Seeding with epithelial cells may possibly lead to synthesis of an epithelial tissues but the stroma will still be missing because it requires the presence of an active scaffold that can induce changes in the phenotype of contractile fibroblasts.

D. Induced regeneration consists of two steps: wound contraction blocking and synthesis of new stroma. The expected efficacy could be high since the substance will probably result in contraction blocking, a prerequisite to regeneration. However, in the absence of a scaffold that can act as a template for synthesis of new stroma, it is questionable whether new stroma will be synthesized at all. The safety of the substance is unknown and it must therefore be assumed to be low and that it requires testing for toxicity.

E. This scaffold is DRT, which is known to lead to regeneration of the stroma. Epithelial tissue will not be specifically induced to regenerate by use of the unseeded scaffold. However, for a small-area wound, as this 2 x 2 mm² wound is, it is expected that epithelial tissue will migrate from the wound edges toward the wound center, with synthesis of the epithelial tissue and spontaneous synthesis of basement membrane. (This process works well with skin wounds that have been grafted with a keratinocyte-seeded DRT.) Efficacy should be high. Since all three tissue types will be synthesized. Safety should also be high since this scaffold has passed clinical trials in its use as a device that regenerates skin and peripheral nerves.

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