

## Hyaluronic Acid and Derivatives for Tissue Engineering

Farid Mena<sup>1</sup>, Abder Mena<sup>2</sup> and Bouzid Mena<sup>1\*</sup>

<sup>1</sup>Fluorotronics, Inc, Departments of Life Sciences, Chemistry and Nanobiotechnology, 2453 Cades Way, Bldg C, San Diego, CA 92081, USA

<sup>2</sup>Centre Medical des Guittieres, Departments of Aesthetic and Anti-Aging Medicine, Rue des Guittieres, Saint-Philbert de Grand lieu 44310, France

Corresponding Author: Dr. B Mena, Fluorotronics, Inc, Departments of Life Sciences, Chemistry and Nanobiotechnology, 2453 Cades Way, Bldg C, San Diego, CA 92081, USA, E-mail: bouzid.mena@gmail.com, dr.fmena@gmail.com

Among the protein-based hydrogel-forming polymers, various salts of hyaluronic acid (HA), aka hyaluronan or sodium hyaluronate, are used to prepare tissue-engineering. HA is a natural occurring glycosaminoglycan, a polysaccharide of high molecular weight which displays interesting viscoelastic properties. Among other organisms, HA is omnipresent in the human body, occurring in almost all biological fluids and tissues, although the highest amounts of HA are found in the extracellular matrix of soft connective tissues. HA is synthesized in a unique manner by a family of hyaluronan synthases and degraded by hyaluronidases and, exerts pleiotropic biological functions such as tissue repair and tissue regeneration. The excellent biocompatibility and biodegradability of HA-derived hydrogels make them ideal materials for tissue engineering. Nevertheless, because of their hydrophilic nature, further modification with adhesion-mediating peptides is required to allow sufficient cell attachment. Hence, several methods of chemical cross-linking using different linkers have been investigated to improve the mechanical properties of those materials for long-term applications in the biomedical field. This manuscript provides an overview of HA and derivatives used as biomaterial scaffold for theranostic medicine.

Over the past three decades, tissue engineering (TE) and regenerative medicine have emerged in order to find alternative therapies to organ transplants, a life-threatening medical procedure. Indeed, tissue loss and organ failure alternatives represent one of the greatest challenges in human health-care avoiding (i) severe drawbacks due to the huge demand for organs, (ii) scarce number of donors and, (iii) life-term medication (e.g. immunosuppressive drugs).

TE is an interdisciplinary field which applies the principles of engineering and life sciences towards developing biological substitutes which restore, maintain, or improve tissue function. One of the major approaches in TE is to deliver cells and/or bioactive substances (e.g. growth factors) to patients using three-dimensional scaffolds. Cells and growth factors are chosen based on the type of tissue to be restored, and the scaffolds should function as temporary artificial extracellular matrices (ECM) which accommodate the cells and guides their growth in three dimensions to form new tissue.

Polymers are ideal candidates as scaffold materials for TE since they can be tailored to have desired properties (e.g. mechanical features, geometrical shapes, biocompatibility, minimal

toxicity) and, be degraded in the same rate as new tissue is formed. They are represented either by synthetic or natural molecules. For instance, synthetic polymers such as poly(*N*-isopropylacrylamid) (PNIPAM), poly(vinyl alcohol) (PVA) [7,8] and poly(ethylene glycol) (PEG), have been widely explored because of their relatively simple modification to prepare gels with desired mechanical and physical properties. Natural polymers such as collagen type-I, fibrin, alginate, chitosan, chondroitin sulfate and HA have been used to prepare hydrogel scaffolds. Hydrogels of naturally derived polymers have the advantage of biodegradability and resemble to the natural ECM. Nevertheless, some of them have also their limitations. Thereby, collagen hydrogels can be immunogenic while fibrin hydrogels can yield insoluble fibrin peptides aggregates and can be associated with a certain degree of shrinkage when used as matrices for cell encapsulation.

HA is a glycosaminoglycan (GAG), a polysaccharide that contains no protein backbone and which is receiving special attention in a wide range of biomedical and TE applications. Indeed, this main component of ECM is naturally involved in tissue repair, and displays unique physical-chemical properties (e.g. viscoelasticity, biodegradability, biocompatibility), making it an ideal material for TE. Over the years, HA has been isolated from rooster combs or, through microbial fermentation. Today the production and purification of HA has turned into an industry. Highly pure HA is available in a wide range of molecular weights at relatively low costs. However, due to the short turnover rate and limited mechanical properties of native HA solutions, chemical modifications are required to obtain suitable stable biomaterials (e.g. hydrogels for *in vivo* tissue repair). Thereby, methods of chemical crosslinking using different linkers have been investigated.

### Conclusion:

HA is a naturally occurring polysaccharide which is present in extracellular matrices of soft connective tissues and body fluids. With regards to its mechanism of synthesis, its size and its physical-chemical properties, HA is unique among other glycosaminoglycans. HA is able to interact with other macromolecules (e.g. proteins) and, participates in regulating the cell behavior during numerous morphogenic, restorative, and pathological processes in the body. The role of HA in diseases, such as in various forms of cancers, arthritis and

osteoporosis, is leading to new impetus in research and development. The preparation of the safest and efficient HA-based biomaterials for theranostic medicine for any type of lesions, regardless their surface, remains an exciting challenge.