

# Chronology of Bioactive Glass Development and Clinical Applications

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## ABSTRACT

The key research and development steps for bioactive glass (45S5 Bioglass) are documented from the date of discovery in 1969 through FDA approvals of the first dental, ENT, maxillo-facial and orthopedic clinical products. Understanding the mechanisms and quantifying the rapid surface reactions to form a bone-bonding hydroxyl-carbonate apatite (HCA) layer on the bioactive glass in contact with living bone was a vital part of the early development of this class of biomaterials. A key later discovery was enhanced osteogenesis and *in situ* bone regeneration by controlled release of ionic dissolution products from the bioactive glass particulates that leads to up-regulation and activation of seven families of genes, a process called osteostimulation.

**Keywords:** Bioactive Glass; 45S5 Bioglass; Hydroxyl-Carbonate Apatite (HCA); Bone-Bonding; Osteogenesis; Regeneration; Genes, Dental; ENT; Maxillo-Facial; Orthopedics; Clinical; Osteostimulation

## 1. Introduction

This paper documents a field of glass research and development pioneered over the last 40 years that has greatly enhanced the length and quality of life. One of the first major developments leading to saving of life was the optical microscope. Invention of the microscope using glass spheres to focus light on objects was the seminal step towards discovering microscopic life forms of bacteria, viruses and fungi, e.g. pathogens. This discovery led to treatment and eventually elimination of many diseases that was instrumental in creating the improvements in public health and healthcare that occurred in the 19<sup>th</sup> and 20<sup>th</sup> centuries. This enormous social change can be termed a revolution in Life Preservation. A major consequence of life preservation was an expansion of the human lifespan from an average of 45 years to 80+ years. It is projected that by 2050 there will be more than 1 billion people alive on earth aged 60 years old or older.

A second revolution in healthcare has occurred during the last 50 years, *i.e.* a revolution in Tissue Replacement. From the age of 30 years old onwards, all tissues progressively deteriorate. Thus, an increase in length of life is usually accompanied by a decrease in quality of life. To repair, replace and restore the function of hips, knees, eyes, ears, teeth, hearts, kidneys, etc. is now commonplace. Human “spare parts” is a huge business worth tens

of billions of dollars.

The first generation of materials used for tissue replacement was selected by surgeons and materials scientists and engineers to be as biologically inert as possible, therefore they are called bio-inert materials. Corrosion resistant metals and insoluble, non-toxic polymeric materials became the standard biomaterials. However, all bio-inert materials are a compromise because of the incompatibility of the interface between the material and living tissue. Tissue breakdown and loosening over time is a common mode of failure of devices made from bio-inert materials. Stress shielding due to mis-match of elastic moduli of high strength biomaterials and bone leads to resorption of bone and long term implant failure and revision surgeries. Wear of articulating surfaces also leads to creation of wear debris and osteolysis leading to degradation of the interfacial supporting bone.

An alternative, second generation concept for tissue replacement using a special type of glass was discovered in 1969. This concept of “bioactivity” has made it possible to expand greatly the approaches taken in tissue replacement. Bioactive materials form a bond with living tissues. The objective of this paper is to document the chronology of discovery and development of bioactive glasses to become an important range of clinical materials used worldwide for tissue replacement and regenera-

tion. The first part of this paper discusses the mechanism of bioactive bonding and *in vitro* and *in vivo* evidence generated to achieve governmental regulatory approval of clinical uses of 45S5 Bioglass. The second part of the paper documents the clinical applications of bioactive glasses and glass-ceramics. Recent research has discovered that glasses with especially high levels of bioactivity can also be used to activate genes to stimulate the body to repair itself. This discovery has led to the concept of using slowly resorbable bioactive glasses as a third generation of biomaterials designed for tissue regeneration. The third part of the paper discusses the concept of genetic control of tissue regeneration and long term advantages.

## 2. Discovery of Bioactive Glasses

For millennia it was accepted that any man-made material in the body would result in a foreign body reaction and formation of non-adherent scar tissue at the interface with the material. Thus, initial emphasis on biomaterials for use in the body was on materials that were as inert as possible when exposed to a physiological environment. Prevention of corrosion of metals or degradation of polymers was the primary design objective. This first generation biomaterials approach to replacement of tissues was irreversibly altered when a special composition of soda-lime-phosphate-silicate glass was made by the author and implanted in the femurs of rats in 1969 by Dr. Ted Greenlee and colleagues at the University of Florida [1-3]. The glass composition contained 45% SiO<sub>2</sub>, in weight % with network modifiers of 24.5% Na<sub>2</sub>O and 24.5% CaO. In addition 6% P<sub>2</sub>O<sub>5</sub> was added to the glass composition to simulate the Ca/P constituents of hydroxyapatite (HA), the inorganic mineral phase of bone, **Table 1**.

The glass composition was denoted as 45S5 to signify

**Table 1. Composition of bioactive glasses and glass-ceramics used for medical and dental applications.**

Composition (wt%)	45S5 Bioglass (NovaBone)	S53P4 (AbminDent1)	A-W Glass-ceramic (Cerabone)
Na <sub>2</sub> O	24.5	23	0
CaO	24.5	20	44.7
CaF <sub>2</sub>	0	0	0.5
MgO	0	0	4.6
P <sub>2</sub> O <sub>5</sub>	6	4	16.2
SiO <sub>2</sub>	45	53	34
Phases	Glass	Glass	Apatite beta-wollastonite Glass
Class of bioactivity	A	B	B

the weight % of silica (S) as the network former and a 5-fold ratio of Ca/P. The glasses did not form interfacial scar tissue isolating them from the host femoral bone, and could not be removed from their implant site [1-3]. This discovery led to the development of a new class of biomaterials, called bioactive materials, for use in implants or prostheses and repair or replacement of bones, joints and teeth. **Table 2** summarizes the chronology of the development of bioactive glasses as a second generation of biomaterials. The discovery in 1969 was published as a peer reviewed paper in 1971 [1]. This seminal paper describes the composition of the glass and the evidence of bonding to bone by use of transmission electron microscopy (TEM) that reveals the bonded interface as a layer of growing bone mineral that has interdigitated with collagen fibrils generated by osteoblasts growing at the interface. In this first paper an acellular *in vitro* model of the glass samples in a calcium phosphate-rich solution showed by X-ray diffraction (XRD) the steps of growth of a biologically active hydroxyapatite crystal phase on the surface of the glass that mimics the XRD pattern of the HA phase in living bone. Details of the bone-bonded interface are described in a second set of papers in 1971-1972 [2,3].

## 3. Compositions of Bioactive Glasses

Bioactive materials, including bioactive glasses [1-3] and glass-ceramics [4-6], are special compositions made typically from the Na<sub>2</sub>O-CaO-MgO-P<sub>2</sub>O<sub>5</sub>-SiO<sub>2</sub> system (**Table 1**). All of the compositions in **Table 1** form a mechanically strong bond with bone. Details are described in [7-15]. The rate of bone bonding depends upon composition of the material. Glass compositions with the fastest rates of bone bonding also bond to soft tissues [16].

Bioactive materials are used as bulk implants to replace bones or teeth, coatings to anchor orthopaedic or dental devices or in the form of powders, as bone grafts, to fill various types of bone defects. When a particulate of bioactive glass is used to fill a bone defect the rate and quantity of bone regeneration depend on the material's composition [7-15].

Compositions such as 45S5 Bioglass with high rates of bioactivity produce rapid regeneration of trabecular bone with an amount, architecture and bio-mechanical quality of bone that matches that originally present in the site. The rapid regeneration of bone is due to a combination of processes called osteostimulation and osteoconduction [16-19]. Large differences in rates of *in vivo* bone regeneration and extent of bone repair indicate that there are two classes of bioactive materials (**Table 1**) [16-19].

## 4. Classes of Bioactivity

Class A bioactivity leads to both osteoconduction and

**Table 2. Chronology of science and clinical product development of 45S5 bioglass.**

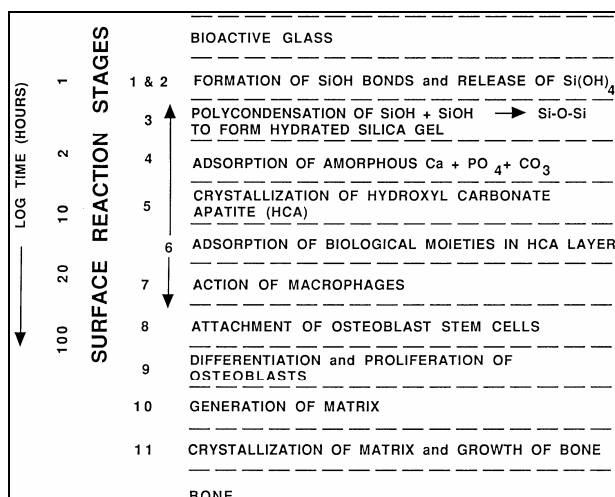
1969	Discovery of bone bonding to 45S5 Bioglass at University of Florida [Report to US Army Medical RD Command]
1971	First peer reviewed publications of bonding of bone to bioactive glasses and glass-ceramics [1-3]
1972	Bonding of Bioglass bone segments and coated femoral stems in monkeys [9,10]
1975	Bioglass coated alumina bone bonding to sheep hip implants (in Germany) [11]
1977	Bonding of Bioglass implant in guinea pig middle ear [17]
1977	Patent applications filed for Bioglass coatings on metals and alumina ceramics [17]
1981	Discovery of soft connective tissue bonding to 45S5 Bioglass [16]
1981	Toxicology, biocompatibility studies (20 <i>in vitro</i> and <i>in vivo</i> ) to establish safety for FDA clearance of Bioglass products [16]
1985	First medical product (Bioglass Ossicular Reconstruction Prosthesis) (MEP) cleared by FDA via the 510 (k) process [17,35-38]
1987	Discovery of osteoproduction (osteostimulation) in use of Bioglass particulate in repair of periodontal defects [17,39,43]
1988	Bioglass Endosseous Ridge Maintenance Implant (ERMI) cleared by FDA via the 510 (k) process [17,31-34,40,41]
1991	Develop sol-gel process method to make bioactive gel-glasses extending bioactive compositional range of bioactivity [45,46]
1993	Bioglass particulate for use in bone grafting to restore bone loss from periodontal disease in infrabony defects (Perioglas) cleared by FDA via the 510 (k) process [17]
1995	Perioglas obtained CE Mark in Europe [17]
1996	Use of Perioglas for bone grafts in tooth extraction sites, alveolar ridge augmentation cleared by FDA via the 510 (k) process [17,39,43]
1999	European use of 45S5 particulate for orthopedic bone grafting (NovaBone) [17,33,42]
2000	FDA clearance for use of NovaBone in general orthopedic bone grafting in non-load bearing sites [17,33,42]
2000	Quantitative comparison of rate of trabecular bone formation in presence of Bioglass granules versus synthetic HA and A/W glass-ceramic [14]
2000	Analysis of use of 45S5 Bioglass ionic dissolution products to control osteoblast cell cycles [22,25]
2001	Gene expression profiling of 45S5 Bioglass ionic dissolution products to enhance osteogenesis [26,27]
2004	FDA clearance of 45S5 particulate for use in dentinal hypersensitivity treatment (NovaMin) [17,44]
2005	Development of variety of dental maintenance products (NovaMin) [17,44]
2009	Anniversary of 1 million doses of NovaBone bone graft product and 1 million tubes of NovaMin toothpaste
2011	Acquisition of NovaMin technology by Glaxo-Smith-Kline and world launch of Sensodyne Repair and Protect toothpaste for prevention of dentinal hypersensitivity and gingivitis

osteostimulation as a consequence of rapid reactions on the bioactive glass surface [16-19]. The surface reactions involve dissolution of critical concentrations of soluble Si and Ca ions that give rise to both intracellular and extracellular responses at the interface of the glass with its physiological environment. The intracellular and extracellular response of osteoprogenitor cells results in rapid formation of osteoid bridges between particles, followed by mineralization to produce mature bone structures [17,19]. Rates of osteoproduction of various bioactive particulates have been quantified by Oonishi *et al.* that provide the fundamental *in vivo* comparisons of Class A vs. Class B bioactive materials [14].

## 5. Bioactivity Reaction Stages

New surface and interfacial analyses techniques were developed to understand the mechanisms and kinetics of

bioactive reactions *in vitro* and *in vivo* [1,8,12,13,20-23]. These methods showed that there is a sequence of eleven reaction stages that occur at the surface of a Class A bioactive glass. **Figure 1** indicates in the log time axis that the first five stages of surface reactions occur very rapidly and go to completion within 24 hours for the bioactive glasses with highest levels of bioactivity, e.g. 45S5 Bioglass. The effect of the surface reactions is rapid release of soluble ionic species from the glass into the interfacial solution. A high surface area composed of hydrated silica and polycrystalline hydroxyl-carbonate apatite (HCA) bi-layer is formed on the glass surface within hours (Stages 1-5). The reaction layers enhance adsorption and desorption of growth factors (Stage 6) and decrease greatly the length of time macrophages are required to prepare the implant site for tissue repair (Stage 7).



**Figure 1.** Sequence of interfacial reactions between bone and a class A bioactive glass or glass-ceramic.

Attachment of stem cells (Stage 8) and synchronized proliferation and differentiation of the cells, (Stage 9) rapidly occurs on the surface of Class A bioactive materials [12,15-17,24-30]. Several weeks are required for similar cellular events to occur on the surface of bio-inert and Class B bioactive materials. Differentiation of progenitor cells into a mature osteoblast phenotype does not occur on bio-inert materials and is rare on Class B bioactive materials because of the lack of ionic stimuli. In contrast, osteoprogenitor cells colonize the surface of Class A bioactive materials within 24 - 48 hours and begin production of various growth factors which stimulate cell division, mitosis, and production of extracellular matrix proteins, (Stage 10) [24-28]. Mineralization of the matrix follows soon thereafter and mature osteocytes, encased in a collagen-HCA matrix, are the final product by 6 - 12 days *in vitro* and *in vivo* (Stage 11) [12,14-16, 23-28].

## 6. Cell Cycle Control and Gene Activation

There are very few cells in the bones of older people that are capable of dividing and forming new bone. The few osteoprogenitor cells that are present must receive the correct chemical stimuli from their local environment that instruct them to enter the active segments of the cell cycle leading to cell division (mitosis) and eventually regeneration of new bone (osteogenesis). References [25], [28] and [29] summarize the sequence of cellular events that comprise a cell cycle for a single osteoblast progenitor (adult stem) cell and its division into daughter cells and differentiation into mature bone cells.

Resting cells are in the  $G_0$  phase and unless they are stimulated to enter into active phases of the cell cycle they will not lead to bone regeneration. A new cell cycle begins after a cell has completed mitosis. A key to re-

generative repair of bone is to: 1) control the population of cells that are capable of entering into active phases of the cell cycle; 2) complete the mitosis of cells with accurate replication of genes (cell proliferation); and 3) achieve cellular differentiation into a phenotype capable of synthesizing a full complement of extracellular proteins that constitute a mature osteocyte [29,30].

The studies reported by Xynos *et al.* showed that such osteoblast cell cycle control is achieved by the controlled release of ionic dissolution products from 45S5 bioactive glass [23-28]. Osteoprogenitor cells colonize the surface of the bioactive glass; however, the concentration of soluble Si and Ca ions at the cell-solution interface is critical for controlling the cell cycle and activating a series of seven families of genes responsible for osteogenesis. Controlled rates of dissolution of the glass provide the critical concentration of the biologically active ions to the cells via the interfacial solution. The families of genes that are unregulated and/or activated are related to the relevant segments of the cell cycle, cell proliferation and cell differentiation. Details are given in [23-28] and reviewed in [29,30].

## 7. Clinical Applications

**Table 2** summarizes the chronology of the science and development of clinical products from the date of the first discovery of 45S5 Bioglass in November 1969.

A listing of medical and dental products based upon 45S5 Bioglass is given in **Tables 3-5**. Key papers describing development of the clinical products are given in [30-43]. Details are reviewed in [17-19]. Numerous clinical citations are given in [17] for all the products listed in **Tables 3-5**. The year 2009 heralded the 40th anniversary of the discovery of 45S5 Bioglass and the landmark sales of the one millionth dose of the bone graft product (NovaBone and Perioglas). That year also marked sales of the one millionth tube of tooth paste containing 45S5 particulate (NovaMin) designed to oc-

**Table 3. Orthopedics products based upon 45S5 bioglass.**

	Long bone fracture (acute and/or comminuted); alone and with internal fixation
Trauma	Femoral non-union repair Tibial plateau fracture
Arthroplasty	Filler around implants (acetabular reconstruction) Impaction grafting
General	Filling of bone after cyst/tumor removal
Spine fusion	Interbody fusion (cervical, thoracolumbar, lumbar) Posterolateral fusion Adolescent idiopathic scoliosis

**Table 4. Cranial-facial products based upon 4S55 bioglass.**

Cranioplasty	Facial reconstruction
	Extraction sites
	Alveolar ridge augmentation
General oral/dental defects	Sinus elevation
	Cystectomies
	Osteotomies
Periodontal repair	

**Table 5. Dental-maxillofacial-ENT products based upon 4S55 bioglass.**

Toothpaste and treatments for dentinal hypersensitivity
Pulp capping
Sinus obliteration
Repair of orbital floor fracture
Endosseous ridge maintenance implants
Middle ear ossicular replacements (Douek MED)

clude dentinal tubules and remineralize the surface of teeth, thereby eliminating the cause of dentinal hypersensitivity. In 2011 Glaxo-Smith-Kline acquired the NovaMin technology and has launched a superbly successful over the counter version of bioactive toothpaste called Sensodyne Repair and Protect that prevents dentinal pain sensitivity and inhibits gingivitis. It is an example of the use of bioactive materials as a preventative treatment—the latest revolution in healthcare. This technology and method of function of the bioactive glass particulate is described in chapter 31 in [44].

## 8. Bioactive Glasses in Tissue Engineering

In 1991 it was discovered that bioactive glasses could be made using a low temperature sol-gel chemical process [45,46]. A much broader compositional range for bioactivity was possible with bioactive gel-glasses due to the high surface area of the final product [46]. Sol-gel processing also made it possible to produce bioactive gel-glass foams with the highly controlled hierarchical porosity required for cell infiltration into large interconnected 3-D pores, a requirement for viable tissue engineered constructs [47-58]. A comprehensive review by Dr. Julian R. Jones describes development of such TE constructs, historical aspects and other recent topics in this field [58].

## 9. Conclusion

The discovery of bonding of bone to specific composi-

tions of glasses led to a new, second generation of bioactive materials for tissue replacement. Understanding gene activation of human progenitor cells by controlled release of ionic dissolution products from bioactive glasses provides the basis for design of third generation biomaterials that can be used for tissue regeneration. Use of bioactive glass particulate in prevention of oral disease and damage is an example of a fourth generation of biomaterials—bioactive materials for prevention of tissue damage. Bioactive glass science and technology continues to be at the forefront of providing innovative approaches to medicine.

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