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State of TMJ Bioengineering: Working Together Toward Improving Clinical Outcomes

Almarza, Alejandro ; Mercuri, Louis ; Arzi, Boaz ; Gallo, Luigi M ; Granquist, Eric ; Kapila, Sunil ; Detamore, Michael

Abstract: The 6th temporomandibular joint (TMJ) Bioengineering Conference (TMJBC) was held June 14-15, 2018, in Redondo Beach, California, 12 years after the first TMJBC. Speakers gave 30 presentations, and came from the United States, Europe, Asia, and Australia. The goal of the conference has remained to foster a continuing forum for bioengineers, scientists, and surgeons and veterinarians to advance technology related to TMJ disorders. These collective multidisciplinary interactions over the past decade have made large strides in moving the field of TMJ research forward. Over the past 12 years, in vivo approaches for tissue engineering have emerged, along with a wide variety of degeneration models, as well as with models occurring in nature. Furthermore, biomechanical tools have become more sensitive and new biologic interventions for disease are being developed. Clinical directives have evolved for specific diagnoses, along with patient-specific biological and immunological responses to TMJ replacement devices alloplastic and/or bioengineered devices. The 6th TMJBC heralded many opportunities for funding agencies to advance the field: 1) initiatives on TMJ that go beyond pain research, 2) more training grants focused on graduate students and fellows, 3) partnership funding with government agencies to translate TMJ solutions, and 4) the recruitment of a critical mass of TMJ experts to participate on grant review panels. The TMJ research community continues to grow and has become a pillar of dental and craniofacial research, and together we share the unified vision to ultimately improve diagnoses and treatment outcomes in patients affected by TMJ disorders.

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Temporomandibular Joint Bioengineering Conference: Working Together Toward Improving Clinical Outcomes

The sixth temporomandibular joint (TMJ) Bioengineering Conference (TMJBC) was held on June 14–15 2018, in Redondo Beach, California, 12 years after the first TMJBC. Speakers gave 30 presentations and came from the United States, Europe, Asia, and Australia. The goal of the conference has remained to foster a continuing forum for bioengineers, scientists, and surgeons and veterinarians to advance technology related to TMJ disorders. These collective multidisciplinary interactions over the past decade have made large strides in moving the field of TMJ research forward. Over the past 12 years, in vivo approaches for tissue engineering have emerged, along with a wide variety of degeneration models, as well as with models occurring in nature. Furthermore, biomechanical tools have become more sensitive and new biologic interventions for disease are being developed. Clinical directives have evolved for specific diagnoses, along with patient-specific biological and immunological responses to TMJ replacement devices alloplastic and/or bioengineered devices. The sixth TMJBC heralded many opportunities for funding agencies to advance the field: (1) initiatives on TMJ that go beyond pain research, (2) more training grants focused on graduate students and fellows, (3) partnership funding with government agencies to translate TMJ solutions, and (4) the recruitment of a critical mass of TMJ experts to participate on grant review panels. The TMJ research community continues to grow and has become a pillar of dental and craniofacial research, and together we share the unified vision to ultimately improve diagnoses and treatment outcomes in patients affected by TMJ disorders. [DOI: 10.1115/1.4044090]

41 Introduction

42 A dozen years after the first temporomandibular joint (TMJ)
 43 Bioengineering Conference (TMJBC) [1], the TMJ, or jaw joint,
 44 the number of publications have risen (Fig. 1), yet there is still a
 45 lack novel diagnostic tools or clinical therapies. The main symp-
 46 tom that leads TMJ patients to seek medical treatment continues
 47 to be pain or jaw dysfunction [2–4]. In terms of TMJ research
 48 integration with other fields of science, there is still a lack of a
 49 strong presence in either the dental or orthopedic fields. The
 50 American Association of Dental Research (AADR) and the Inter-
 51 national Association of Dental Research (IADR) both feature
 52 TMJ research in a sporadic and diffuse manner, spread over dif-
 53 ferent research groups. Moreover, the representation of TMJ
 54 research in the Orthopedic Research Society (ORS) is even
 55 sparser than at the AADR or IADR. Hence, there is an opportunity
 56 to promote concentrated/dedicated sessions for TMJ research.

Therefore, one of the continuing missions of the TMJBC has been
 to unite TMJ clinician, veterinarian, engineer, and biologist
 researchers across disciplines to increase the visibility of the TMJ
 field.

The format of the TMJBC meeting has evolved from the first to
 the most recent sixth event². The first conference in 2006 was
 funded by the National Institute of Dental and Craniofacial
 Research (NIDCR), with an extensive list of invited speakers
 documented in a 2007 publication in the *Annals of Biomedical
 Engineering* [1]. At the sixth TMJBC, speakers were selected
 from unsolicited abstracts and were then assigned a 15-min oral
 podium presentation. Presentations at the sixth TMJBC were
 organized into six areas of emphasis: Clinical studies, biome-
 chanics, natural occurring TMJ disorders in animals, animal mod-
 els of degeneration, biological basis for disease and treatments,
 and tissue engineering. There was time for group discussion of
 each topic, leading to general consensus on the cutting edge of
 technologies, gaps in the research, and the need for more

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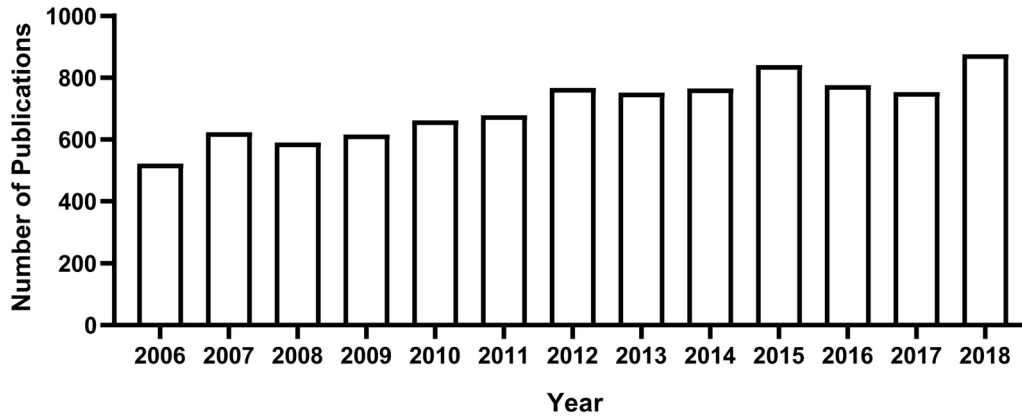


Fig. 1 Number of publications from PubMed with the key terms “TMJ” from 2006 to 2018

75 standardized clinical and research approaches to the diagnosis and
76 management of TMJ disorders.

77 The objectives of this publication are to provide an overview
78 of the last conference, to highlight changes in the landscape of
79 publications/grants since the first TMJBC, to attract new talent
80 and established investigators to the field, and to call for policy
81 advancements to grow the TMJ research community. The follow-
82 ing sections will summarize the presentations for each area of
83 emphasis and indicate where further advances or greater focus is
84 required.

85 **Clinical Studies Session**

86 The clinical directives that emerged from the five prior
87 TMJBCs have matured. The TMJBCs have been influential in
88 moving surgeons toward a more orthopedic approach to the diag-
89 nosis and management of intra-articular TMJ pathology. This
90 orthopedic influence is not only reflected in the abstract presenta-
91 tions at recent TMJBC meetings but also additionally in a contem-
92 porary publication entitled “potential indications for tissue
93 engineering in temporomandibular joint surgery” [5] in which the
94 authors, utilizing both their basic science and clinical expertise,
95 developed patient inclusion and exclusion criteria for partial and
96 total TMJ reconstruction using bioengineered tissue.

97 The following is a synopsis of the clinically related presenta-
98 tions, followed by potential clinical directives that can be drawn
99 from them.

100 **Alloplastic Temporomandibular Joint Replacement.** The
101 sixth TMJBC demonstrated the continued expansion of surgeon
102 mindset to include an evidence-based approach to the manage-
103 ment of TMJ disorders. This migration was particularly evident in
104 presentations related to the management of end-stage TMJ dis-
105 ease, with the dissemination of preliminary results using three
106 new alloplastic total TMJ replacement systems from Australia,
107 Brazil, and India.

108 The Australian TMJ replacement system, from Dr. Dimitroulis’
109 group, utilizes a 3D-printed device with a custom-made direct
110 metal laser sintered metal alloy condyle, all polymer digitally
111 sized glenoid fossa, and custom surgical cutting and placement
112 guides. This device was tested in a cohort study in 38 patients,
113 with the longest follow-up reported to be 24 months (mean
114 15.3 months) [6].

115 The Brazilian TMJ device, from Dr. Genovesi’s group, is an
116 injection-molded TMJ replacement composed of a petroleum-
117 based material: polyether ether ketone (PEEK) LT1 20% Ba.
118 PEEK screws are used to fixate the fossa and short ramus com-
119 ponent to the host bone. To date, seven cases at 100 days were
120 reported.

121 The Indian selective laser melting (SLM), 3D printed, patient-
122 specific TMJ device was reported, by Dr. Mehrotra, to have been

123 developed for the management of TMJ ankylosis and pathology.
124 The fossa component is all-ultrahigh molecular weight polyethyl-
125 ene and the condyle/ramus component was SLM 3D printed tita-
126 nium alloy. Diet and quality of life variables were improved
127 within 3 months in the patient population reported.

128 Although presentations at the TMJBC were not all peer-
129 reviewed, the aforementioned presentations emphasize the global
130 need and opportunity for forward-thinking approaches to TMJ
131 total joint replacement, with lessons of the past [1,5] being
132 increasingly more important as the opportunities for clinical trans-
133 lation become within reach with varying regulatory frameworks
134 worldwide.

135 **Biologic and Immunologic Responses to Temporomandibu-
136 lar Joint Replacement Materials.** The potential biologic
137 responses to material wear from alloplastic devices were
138 described in a presentation by Dr. Mercuri, who reported serum
139 metal levels in some maxillofacial reconstruction patients who
140 had undergone dental implant placement, orthognathic surgery
141 using rigid metal fixation plates and screws, or total alloplastic
142 temporomandibular joint replacement. All control participants had
143 levels below the normal reference range for all serum markers
144 assessed. In the orthognathic group, one patient had an increased
145 serum cobalt level. In the TMJ TJR group, one patient had an
146 increased serum cobalt level and another patient had an increased
147 serum chromium level. In the dental implant group, one patient
148 had an increased serum titanium level and another had increased
149 serum levels of titanium and chromium. The results raise ques-
150 tions regarding the types and magnitude of metal released from
151 maxillofacial reconstruction devices and their potential long-term
152 local and systemic effects [7].

153 Dr. Nadim Hallab, a keynote speaker, discussed immunologic
154 responses to metal particulation due to functional wear associated
155 with TMJ replacement devices, in comparison to hip and knee
156 total joint replacements. Given that <1% of the >1 × 10⁶ people
157 per annum receiving orthopedic total joint replacement implants
158 in the U.S. are not tested for metal sensitivity pre-op or at revis-
159 sion, it is likely that implant-related metal sensitivity has been
160 underreported and remains underestimated. However, the slow
161 and continuing improvements in sensitivity testing will likely con-
162 tinue to provide cumulative clinical evidence into the utility of
163 metal sensitivity testing, along with greater understanding into
164 how and when metal sensitivity develops [8].

165 **Clinical Diagnostic and Therapeutic Studies.** Clinical studies
166 related to the diagnosis and management of temporomandibular
167 joint disorders were reported. The results of a diagnostic electro-
168 myography (EMG) study from Dr. Connelly’s group demonstrated
169 that temporomandibular disorder (TMD) patients had different
170 muscle coordination chewing patterns in the masseter and tempo-
171 ralis muscles compared to normal controls. The TMD patients

172 demonstrated working-side muscle activity that was significantly
173 less than in the normal controls, possibly due to preferred side
174 chewing patterns. The authors felt these data may provide a refer-
175 ence base for further EMG studies in TMD patients [9].

176 A study was presented from Dr. Lund's group that examined
177 the extracellular matrix (ECM) proteins in synovial tissue from
178 patients with internal derangement compared to generalized joint
179 hypermobility and normal joint mobility. While the results dem-
180 onstrated no statistically significant difference in ECM proteins
181 between generalized joint hypermobility and normal joint mobil-
182 ity, patients with internal derangement had significant differences
183 in ECM protein concentrations—indicating TMJ synovial tissue
184 deterioration. These findings may provide synovial fluid markers
185 that might aid in the diagnosis or progressive TMJ disease [10].

186 The difficulty in the differential diagnosis of TMJ chondroma-
187 tosis versus chondrosarcoma was presented by Dr. Levorova.
188 Since the treatments and prognoses of these two pathologic enti-
189 ties are completely different, surgeons and pathologists must be
190 aware of this distinction [11].

191 Therapeutically, results with the use of intra-articular platelet
192 rich plasma (PRP) in the management of TMD pain was presented
193 by Dr. Machon. PRP may effect changes in cell proliferation and
194 regulation of cellular metabolism. This study reported the 5-year
195 follow-up results after PRP injection into the joints of Wilkes IV
196 and V patients. Seven percent of the patients reported no differ-
197 ence in their pain, but 45% experienced the return of their pain
198 within 5 years. The presenter concluded that the major factor in
199 failure of PRP therapy was the duration of patient joint pain
200 before treatment. This study encouraged the important of early
201 diagnosis and management of TMJ pathology [12].

202 Biomechanics Session

203 This session provided an update on recent and ongoing biome-
204chanical studies related to the TMJ, mainly with regard to joint
205 loading and its consequences. The first presentation, by Dr. Gallo,
206 addressed the possible mechanical cause of degenerative joint dis-
207 ease and the puzzling gender bias with women being affected by
208 TMJ disorders more often than men in patient studies. TMJ
209 dynamical loading areas were characterized by parameters associ-
210 ated with the energy density spent in the TMJ. In 200 TMJs of
211 females and males (aged 20–40yr), the data suggested that
212 females performed mandibular movements stressing TMJ soft tis-
213 sue with a higher energy density than in males. According to Dr.
214 Gallo, this significant difference was due primarily to the smaller
215 volumes stressed in female joints compared to males. Joint incon-
216 gruity may play a role so that asymmetric mandibular movements
217 likewise increase energy density spent in TMJ soft tissues.

218 The second contribution, from Dr. Mesnard, presented a novel
219 image processing method for the characterization of cortical and
220 cancellous bone in the mandibular ramus to be used in finite ele-
221 ment method (FEM) analyses. This method was developed with
222 the aim of providing patient-tailored information for the design
223 and planning of TMJ replacement device implantation.

224 Finally, the third communication by Dr. Sagl addressed TMJ
225 modeling concepts with the aim of performing FEM analyses of
226 mechanical loading. The study presented was based on a combina-
227 tion of computed tomography (CT) and magnetic resonance imag-
228 ing (MRI), thus providing information regarding bone and soft
229 tissues. Soft tissues were studied with MRI at different mandibular
230 positions in order to detect, in particular, TMJ disk and masticatory
231 muscle deformations. By using Hill-type muscle [13] as well
232 as biphasic cartilage models, it was possible to investigate the
233 effects of different movement and force patterns on TMJ loading.

234 The biomechanics session presented work in progress based on
235 research performed in centers that have traditionally studied the
236 TMJ by developing pioneering methods [14–18]. New data
237 obtained on larger subject samples are providing foundational
238 data showing different loading patterns for different diagnostic
239 groups, in particular, those with myogenous and arthrogenic pain.

240 However, this research needs to be closely connected to those of
241 TMJ tissue biology. Indeed, previous studies have begun looking
242 at soft tissue mechanics, but changes due to tissue degeneration
243 are still greatly understudied. Research mimicking TMJ loading in
244 live tissue and determining its biological response is still in its
245 infancy and would benefit from further investigation.

Natural-Occurring Temporomandibular Joint Damage in Animals Session

248 In recent years, it has become clear that animals, like humans,
249 develop a spectrum of naturally occurring TMJ disorders such as
250 osteoarthritis (OA), ankylosis, luxation, fracture, and neoplasm
251 [19–21]. Although the anatomic and physiologic features of the
252 TMJ may differ between humans and animals, these naturally
253 occurring diseases may have similar or identical pathogeneses to
254 the disorder in humans [22]. Specifically, studying TMJ disorders
255 that naturally occur in animals may elucidate not only on the
256 pathogenesis of the disorder but also its response to similar ther-
257 apeutic interventions intended for human use. There were several
258 presentations on naturally occurring TMJ disorders in domestic
259 and wild animals.

260 **Naturally Occurring Temporomandibular Joint Osteoar-**
261 **thritis in Domestic Dogs.** Dr. Arzi presented on recent studies
262 examining naturally occurring TMJ disorders in dogs and cats,
263 presenting that TMJ osteoarthritis is most common in dogs when
264 compared to cats [19]. Furthermore, characterization of TMJ
265 osteoarthritis in dogs revealed that, as in humans, the mechanical
266 properties of the TMJ disk are negatively influenced by arthritic
267 conditions as the spectrum of arthritic pathological processes
268 exhibited in dogs include articular surface fibrillation, subchondral
269 bone defects and sclerosis, osteophyte formation, and disk perfor-
270 ation [21]. From a clinical perspective, the manifestation of TMJ
271 osteoarthritis in dogs is similar to humans in the sense that clinical
272 symptoms may not correlate with the presence and severity of CT
273 findings [19,23].

274 **Naturally Occurring Temporomandibular Joint Osteoar-**
275 **thritis in Horses.** The horse is a large animal model that experi-
276 ences naturally occurring TMJ disorders. For example, like
277 humans, horses experience an age-related degeneration in the
278 form of intra-articular disk dystrophic mineralization [24]. In
279 addition, as observed in dogs, cats, and human, horses exhibit
280 TMJ fractures and osteoarthritis. In his presentation entitled
281 “regional and disease-related differences in properties of the
282 equine TMJ disease,” Dr. Derek Cissell demonstrated that natu-
283 rally occurring degenerative changes in the TMJ of horses may
284 impact the compressive stiffness of the TMJ disk in a region-
285 dependent fashion. In addition, he demonstrated that the horse's
286 age, the region of the TMJ, and the specific degenerative changes
287 may all influence the composition and mechanical properties of
288 the equine TMJ disk. These results indicated that future studies
289 should determine how the equine TMJ withstands mediolateral
290 forces during mastication, the consequences of altered TMJ disk
291 composition, and the influence of compressibility for overall joint
292 function and in the pathophysiology of TMJ arthritis in horses.

293 **Naturally Occurring Temporomandibular Joint Osteoar-**
294 **thritis in Wildlife.** Dr. Frank Verstraete detailed TMJ arthritis in
295 wildlife via a series of comprehensive studies and publications
296 that examine museum specimens. The most commonly affected
297 species in the western United States include the California sea
298 lion (63.5%), walrus (60.5%), and the American black bear (50%)
299 [25–27]. Interestingly, this particular study found that some carni-
300 vores (such as the California bobcat and gray fox) did not exhibit
301 TMJ arthritis [28]. In species that exhibit moderate to serve TMJ
302 arthritis, it is assumed that the disease was associated with a cer-
303 tain degree of discomfort and impaired function. It was concluded

304 that, while the exact etiology or pathophysiology of TMJ arthritis
305 in wildlife remains elusive, the disease may contribute to morbidity
306 and mortality.

307 Since naturally occurring disease reflects the complex genetic,
308 environmental, and physiological variation present in the human
309 population, it is plausible that better understanding of TMJ disorders
310 in animals will lead to a better understanding of TMJ disorders
311 in humans, or at least reaffirm existing findings and concepts.
312 On a similar note, clinical trial-based studies utilizing naturally
313 occurring TMJ disorders as a model can be informative for transla-
314 tion of new treatment modalities.

315 Animal Models of Degeneration Session

316 The clinical presentation of pain-free TMJ osteoarthritis is often
317 of limited clinical significance. It has been recognized that up to
318 20% of the population has evidence of TMJ osteoarthritis on
319 imaging without clinical signs or symptoms of disease [29]. Fol-
320 lowing lower back pain, TMJ discomfort is the second most com-
321 mon musculoskeletal pain disorder with an associated annual cost
322 estimated at \$4 billion [30]. Therefore, incorporating pain meas-
323 ures into translational models of TMJ degenerative diseases is
324 critically important.

325 As with most chronic pain conditions, centralized pain mecha-
326 nisms often have a greater contribution to the pain syndrome than
327 the initial inciting disease, making it difficult to replicate in ani-
328 mal models [31]. This interplay between centralized pain mecha-
329 nisms and the inciting disease is evident in the clinical research of
330 TMJ disease with the diagnostic criteria for TMD disease reliance
331 on both axis I characterization of joint and muscle disease and the
332 use of axis II instruments for measuring psychosocial and pain-
333 related disability [32].

334 In TMJBC 6, only one abstract and one poster specifically
335 addressed animal pain and joint disease models. Dr. Almarza's
336 group presented a poster on whether a sudden change in occlusion
337 is associated with the emergence of hypersensitivity in the TMJ
338 area in adult male rats. These results suggest an increased sensitiv-
339 ity to noxious mechanical stimuli following altered TMJ loading.

340 An oral presentation by Megan Sperry from Dr. Winklestein's
341 group presented an animal model of TMJ osteoarthritis and pain
342 that utilized mechanical overload to induce condyle changes and
343 pain. In this study, nine rats underwent mechanical loading of
344 their TMJ with 3.5 N of force. The findings suggest hypoxia and
345 inflammation may be early contributors to pain and structural
346 changes in the rat TMJ.

347 The incorporation of pain assessment in animal TMJ disease
348 models will be important for both the study of acute-to-chronic
349 TMJ pain transition as well as the translation of potential regener-
350 ative medicine interventions to clinical care. Further research into
351 the contribution of both central pain mechanisms and peripheral
352 contributions in TMJ animal models of degeneration is urgently
353 needed to better understand the indications and limitation of medi-
354 cal and surgical management of TMJ chronic pain. Indeed, there
355 is a dearth of science on TMJ pain, and the two studies presented
356 are not the only paths to investigate TMJ pain, indicating the need
357 for more pain mechanisms to be investigated.

358 Biological Basis for Disease and Treatments Session

359 Dr. Sunil Kapila provided an in-depth presentation highlighting
360 that there are several functional and anatomic distinctions associ-
361 ated with the TMJ when compared to those of appendicular joints.
362 These distinctions may partly explain the challenges in restoring
363 the diseased TMJ to health, or in the engineering of its replace-
364 ments. First, mandibular condyle fibrocartilage develops from the
365 neural crest rather than from mesodermal origin as does hyaline
366 cartilage in appendicular joints. Second, the mandible, including
367 the condyles, is formed as a secondary cartilage as opposed to pri-
368 mary cartilage as in the formation of appendicular joints and long
369 bones [33]. Third, mandibular condylar fibrocartilage serves a

hybrid anatomical function of being both an articular and a growth
370 cartilage, which differs from the appendicular skeleton, where
371 these two functions are served by articular hyaline cartilage and
372 the epiphyseal growth plates, separated by an epiphysis. Finally,
373 while the articular surfaces of appendicular joints are lined by
374 hyaline cartilage, that of the TMJ is composed of fibrocartilage
375 [34], with the mandibular condyle consisting of deeper zones of
376 hyalinelike cartilage that is separated from the more fibrouslike
377 superficial zone (SZ) composed of highly aligned fibers of a pro-
378 liferative cellular layer [35,36]. Therefore, TMJ fibrocartilage
379 contains both types I and II collagen [37], whereas the articular
380 hyaline cartilage does not typically contain type I collagen [38].
381 This organization of collagen fiber alignment and type provides
382 the TMJ with the functional characteristic of withstanding tensile
383 loading better than hyaline cartilage. As such, Dr. Kapila
384 explained that the significance of these distinctions to disease ini-
385 tiation and progression between the TMJ and appendicular joints
386 may explain certain genetic disorders that affect every joint in the
387 body while sparing the TMJ [39] as well as the unique age and
388 gender distribution of TMDs [40–44].
389

390 Dr. Kapila then presented an overview of his work on patho-
391 physiologic functions of estrogens that primarily involves signal-
392 ing via estrogen receptors ER- α and ER- β [45]. The
393 preponderance of TMJ problems affects women and their early
394 onset is during reproductive years, as opposed to similar degener-
395 ative conditions in other joints that largely afflict postmenopausal
396 women. These findings have led to the implication of female sex
397 hormones, particularly 17- β estradiol (E2) in TMJ osteoarthritis
398 [40,46]. Indirect evidence for an association between E2 and TMJ
399 diseases is provided by findings of elevated serum E2 in subjects
400 with TMJ disease [46,47], the presence of the ERs in the TMJ of
401 females [48], and the association of ER- α polymorphisms that
402 enhance ER- α levels with the prevalence and severity of TMJ OA
403 [49–54]. Dr. Kapila's ongoing studies are exploring in vivo the
404 contributions of E2, ER- α and candidate matrix metalloprotei-
405 nases to the targeted loss of TMJ matrices and their contribution
406 to TMJ OA specifically, but not of appendicular joint OA.

407 Additionally, this session highlighted work from Dr. Yadav
408 Sumit's group with three different presentations. The objective of
409 their research effort was to characterize the long-term effects of
410 intermittent parathyroid hormone (I-PTH) delivery on the mandib-
411 ular condylar cartilage and subchondral bone, in vitro, and in
412 mice. They reported that there was a significant increase in bone
413 volume, tissue density, mineral deposition, tartrate resistant acid
414 phosphatase activity, cell proliferation, and cartilage thickness in
415 the I-PTH treated mice when compared to a control group. In their
416 second presentation, they described the effects of simultaneous
417 injections of the I-PTH and alendronate on the mandibular condy-
418 lar cartilage and the subchondral bone in a mice model. The find-
419 ings suggested that the effects of alendronate on mandibular
420 condylar cartilage may be similar to the effects of I-PTH. How-
421 ever, the effects of simultaneous injections of both I-PTH and
422 alendronate were more pronounced in the subchondral bone. The
423 final presentation aimed to determine the effects of bone morpho-
424 genetic protein (BMP-2) loss of function on the cartilage and sub-
425 chondral bone of the TMJ. It was found that deletion of BMP-2 in
426 aggrecan-expressing cells during postnatal development may lead
427 to cartilage breakdown and early development of OA.

428 The works by Dr. Kapila and Dr. Sumit highlight the need to
429 tailor and design treatment therapies for the TMJ differently than
430 orthopedic joints. PTH based therapies are often targeted for
431 osteoporosis and mainly in females. As such, there is an opportu-
432 nity to discover similar links between PTH-based therapies and
433 TMJ soft tissues.

Tissue Engineering Session 434

435 Since the first TMJBC, the group of investigators focused on
436 TMJ tissue engineering has remained small. The main contribu-
437 tions have come from the original organizers Dr. Athanasios

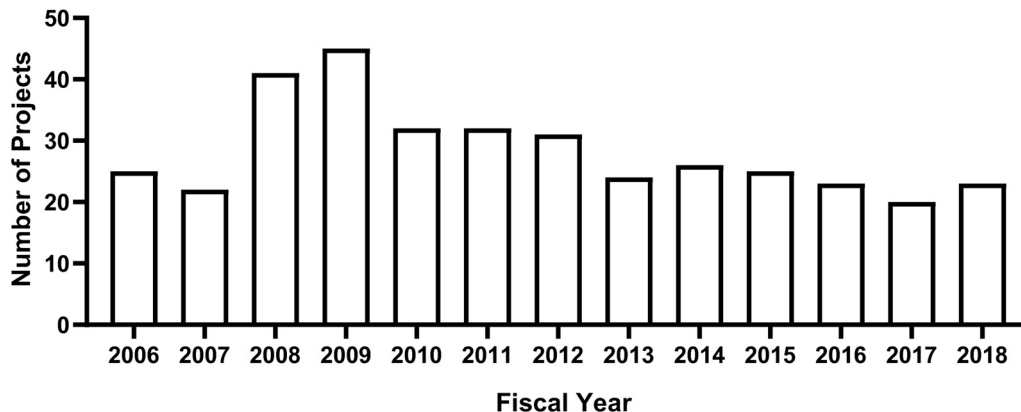


Fig. 2 Number of R01 funded projects from NIH Reporter with the key terms TMJ from 2006 to 2018

438 [55–58], Dr. Detamore [36,59], Dr. Jeremy Mao [60], Dr. Scott
 439 Hollister [61,62], and from Dr. Almarza [63–65]. Nevertheless,
 440 profound advances have been made by these researchers in the
 441 engineering of both a TMJ disk and mandibular condyle. In terms
 442 of the TMJ disk, it now has been shown in animal models that
 443 focal defects can be repaired and heal [55], and whole disks can
 444 be replaced with scaffold that remodel to become a tissue with
 445 many similarities to the native TMJ disk [65]. These studies have
 446 shown that both approaches are feasible for the treatment of
 447 patients with clinical indications for regenerative therapies. In
 448 terms of the mandibular condyle, advances in polymer gradients
 449 have regenerated bone in the condyle of rabbits [59] and the soft
 450 tissue of the condyle in goats [63]. Overall, these studies draw the
 451 field ever closer to create a condyle-disk composite bioengineered
 452 replacement implants. Despite these breakthroughs, there are still
 453 concerns with the attachment of these implants and their ability to
 454 withstand the early shear and torque during mandibular functional
 455 loading. More importantly, as discussed elsewhere [5], the patient
 456 will need to be selected carefully, as comorbid conditions could
 457 play a role in healing. Further, concerns with metaplasia, ossifica-
 458 tion, and angiogenesis may be considerations for specific patients.

459 At the sixth TMJBC, presentations were focused on condyle
 460 regeneration, mesenchymal stem cells (MSCs) in scaffolds, and a
 461 scaffold-free cell sheet for TMJ disk focal defects. Specifically,
 462 for mandibular condyle regeneration, Dr. Detamore's Team devel-
 463 oped a combinational 3D printer for TMJ tissue engineering of the
 464 mandibular condyle that incorporates natural materials, such as
 465 devitalized cartilage, demineralized bone, hydroxyapatite, and
 466 pentanoate-functionalized hyaluronic acid with polycaprolactone
 467 (PCL) to create anatomically precise, patient-specific mandibular
 468 condyle bioengineered replacement implants. In these 3D-printed
 469 implants, priority was placed on designing both bone and cartilage
 470 regions to promote cell-infiltration, with supporting preliminary
 471 data presented.

472 Dr. He's group presented a scaffold-free cell sheet technology
 473 to regenerate condylar cartilage by combining bone marrow stro-
 474 mal cells (BMSCs) with condylar chondrocytes. Specifically, high
 475 density coculture of these two cells were tested at different ratios
 476 (Chondrocyte:BMSC = 10:0,7:3,5:5,3:7,0:10). After 3 weeks of
 477 chondrogenesis by micro-environment induction, the 10:0 and 7:3
 478 groups appeared to perform better than the cartilage cell sheets.

479 In another presentation by Dr. He's group, scaffold-free carti-
 480 lage cell sheets covering bone marrow mesenchymal stem cells-
 481 PCL/hydroxyapatite (BMSCs-PCL/HA) scaffolds (cell sheet
 482 group) were transplanted subcutaneously and intramuscularly in
 483 minipigs. The biphasic scaffold group appeared to fail in regenera-
 484 tion because of local nonspecific inflammation led by residual
 485 and degradation products of the PGA/PLA scaffold, while the cell
 486 sheet group appeared to regenerate a healthy osteochondral con-
 487 struct with a mature cartilage layer and closely integrated sub-
 488 chondral structure.

Dr. Helgeland presented work on explaining the effect of the
 angiogenesis inhibitor, angiostatin, on fibrocartilage formation in
 an ectopic rat-model. Collagen type-I scaffolds were divided into
 four groups: (i) scaffold only, (ii) scaffold + BMSCs, (iii) scaffold +
 angiostatin, and (iv) scaffolds + angiostatin + BMSCs. Cell was
 harvested from rat femurs. One construct from each group was
 randomly, subcutaneously implanted in the dorsa of Lewis rats.
 After 2 weeks, biomarkers for inflammation, IL-1 α and IL-1 β and
 vascularization, CD31 appeared to be down-regulated in constructs
 functionalized with angiostatin.

Dr. Natalia Vapniarsky, from Dr. Athanasiou's group, presented
 the first public description of their recent work to develop an
 innovative surgical method—modeling disk thinning with partial
 perforation in a minipig. Specifically, they designed and tested a
 surgical technique for the implantation and stabilization of the
 engineered tissue in situ, and tested in vivo the efficacy of this
 tissue-engineered construct to regenerate surgically created TMJ
 disk defects. As histological evaluation demonstrated that this
 implantation method resulted in more complete TMJ disk defect
 closure than in the untreated control TMJ disk defects. The study
 implantation method induced the formation of fibrous connective
 repair tissue that filled the TMJ disk defect and this repair tissue
 was significantly stiffer in tension than similar tissue in the
 untreated control TMJ disk defects [55].

Dr. Embree's group presented their work on TMJ fibrocartilage
 stem cells (FCSCs) located below the mandibular condyle SZ,
 which can self-organize and can regenerate cartilage and bone. In
 the FCSCs, Wnt/ β -catenin signaling inhibits skeletal stem fate to
 differentiate into chondrocytes and over activation leads to OA,
 but with the addition of a Wnt inhibitor the FCSC population is
 maintained and the fibrocartilage is repaired. The group is looking
 to find the markers that define the TMJ FCSC population and their
 functional role in differentiation, proliferation, and progression of
 TMDs.

The current work on TMJ tissue engineering is cutting edge and
 exciting. However, the small market for TMJ disease management
 options and devices, compared to orthopedics, presents a barrier
 to translation. Other technical barriers are also present, such as the
 efficacy of technologies in a degenerated joint, patient to patient
 variability, etc. Nevertheless, when these technical challenges are
 solved, there will always be a "valley of death" in funding to
 translate TMJ technologies due to the small market. Significant
 funding will be required from industry partners, private donors,
 foundations or the NIH (e.g., R01, SBIR/STTR) to derisk these
 technologies for translation to clinicians and their patients.

Discussion

After six TMJ Bioengineering Conferences, spanning more than
 12 years, it is clear that there is a small, but growing and
 dedicated core of TMJ investigators. This group of investigators

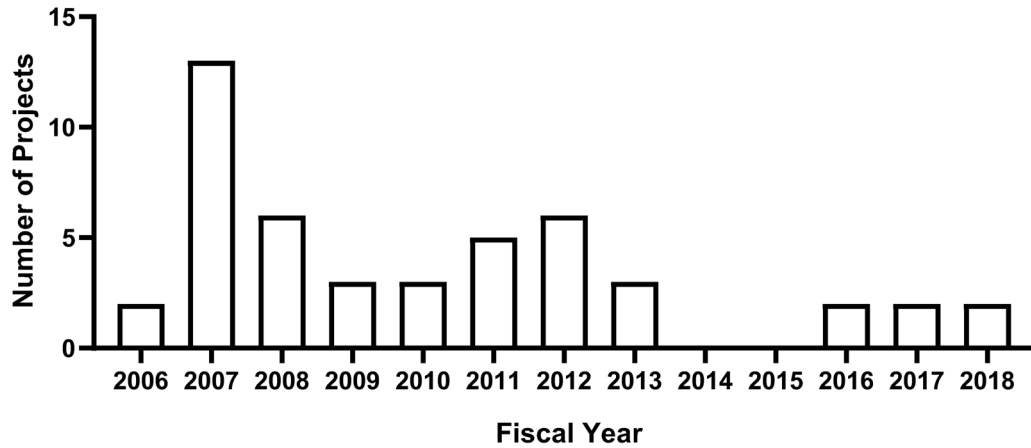


Fig. 3 Number of R21 funded projects from NIH Reporter with the key terms TMJ from 2006 to 2018

538 have been successful in carrying out many of the directives put
 539 forth from the first conference [1], including: Patient specific data,
 540 such as metal allergies; more detailed mechanical models of the
 541 joint; in-depth studies of the naturally occurring TMJ damage in
 542 animals; more biological differences in the TMJ between the
 543 sexes and between the TMJ and other joints; biological therapies
 544 and mechanisms of disease; and in vivo tissue engineering efforts.

545 In the discussions during the conference, a lack of standardized
 546 research methodologies became apparent. For example, a standard
 547 scale to describe the amount of joint damage on histology, such as
 548 the OARSI histopathology scale used for cartilage OA, needs to
 549 be used as-is or adapted to the TMJ. This scale goes from 0 (pristine)
 550 to 6 (full cartilage loss). While the scale can be directly
 551 applied to the TMJ condyle, it will have to be modified to describe
 552 damage to the disk. Another area of standardization could be
 553 mechanical testing, such as displacing at the same percent strain
 554 rate to the same strain step for evaluating engineered tissues or
 555 establishing target loading values for implanted bone regions for
 556 mandibular condyle scaffolds. These changes should be relatively
 557 easy to implement as the community is still small and cohesive.
 558 Furthermore, standardized outcome measures would assist new-
 559 comers to TMJ research in comparing their technologies to the
 560 established benchmarks.

561 Another major topic of discussion was the appropriate target
 562 audience for TMJ research, and the sustainability of current
 563 efforts. TMJ research is not prominent at the ORS, and in general
 564 appears to be more prominent in the dental research community.
 565 TMJ podium sessions at the AADR highlight pain, biomechanics,
 566 and tissue engineering research. However, TMJ research no longer
 567 has a focused research group base at AADR and IADR but is
 568 instead spread over many research groups in an ad hoc fashion.
 569 As an example, formerly there was the IADR “Neuroscience/
 570 TMJ” scientific group, now it is only titled as the “Neuroscience”
 571 group. There was additional concern raised about current Federal
 572 funding. TMJ grants in tissue engineering, TMJ biomechanics,
 573 and TMJ replacement devices are assigned to study sections that
 574 do not typically focus on TMJ research, which may make it difficult
 575 for reviewers to truly assess the significance and innovation
 576 of the proposed work. This can be seen by a decreasing trend of
 577 NIH R01 funded projects on TMJ from 2006 to 2018 and almost a
 578 50% drop from 2009 to 2018 (Fig. 2). Furthermore, the low number
 579 of NIH R21 projects, with an average of less than two projects
 580 per year from 2013 to 2018, indicates a high barrier for entry of
 581 new investigators into the TMJ field and the development of new
 582 lines of research (Fig. 3).

583 As the TMJ Bioengineering Conferences move forward, it is
 584 hoped that interdisciplinary research continues to grow to bring
 585 new diagnostics and therapies to TMJ patients. The group sees
 586 many opportunities for the future. First, initiatives at the NIDCR
 587 for funding TMJ research have arguably been largely focused on

588 pain as highlighted in “The orofacial pain: prospective evaluation
 589 and risk assessment” studies [66–68]. Future request for applica-
 590 tions (e.g., requests for applications) should go beyond pain, such
 591 as ones that will study joint damage and regeneration, which comple-
 592 ments the current NIDCR initiatives. Second, to grow the field,
 593 more training grants are needed for graduate students and fellows
 594 to become engaged in TMJ science. Third, since TMJ tissue engi-
 595 neering solutions have a small market when compared to orthopedic
 596 joints, there is a potential to partner with the Food and Drug
 597 Administration for developing translational bioengineered solu-
 598 tions. Lastly, there is room to grow the pool of TMJ experts on
 599 grant review panels, to the point that a critical mass of researchers
 600 with significant knowledge and experience is able to assess the
 601 significance and impact of groundbreaking TMJ research. The
 602 past 12 years have seen important new contributions in the TMJ
 603 Bioengineering Community, with tremendous opportunity in the
 604 next dozen years ahead.

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