Mone Zaidi   ORCID iD: 0000-0001-5911-9522

Daria Lizneva   ORCID iD: 0000-0002-2901-4268

Kseniia Ievleva   ORCID iD: 0000-0002-0177-234X

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PERSPECTIVE

Beyond Bone Biology: Lessons from Team Science

[1]Mone Zaidi, [1]Daria Lizneva, [1]Sakshi Gera, [1]Charit Taneja, [1]Funda Korkmaz, [1]Anisa Gumerova, [1,2]Kseniia Ievleva, [1]Naseer Ahmad, [1]Vitaly Ryu, [1]Li Sun, [1]Se–Min Kim, [1]Maria I. New, [3]Shozeb Haider, [1]Jameel Iqbal, [4]Clifford Rosen and [1]Tony Yuen

[1]The Mount Sinai Bone Program, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA;

[2]Federal State Public Scientific Institution, Scientific Center for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation;

[3]School of Pharmacy, University College London, London, UK;

[4]Maine Medical Center Research Institute, Scarborough, ME, USA

Correspondence: Mone Zaidi, Email: mone.zaidi@mssm.edu. Fax: 212-426-8312

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ABSTRACT

Today, research in biomedicine often requires the knowledge and technologies in diverse fields. Therefore, there is an increasing need for collaborative team science that crosses traditional disciplines. Here, we discuss our own lessons from both interdisciplinary and transdisciplinary teams, which ultimately ushered us to expand our research realm beyond bone biology.

KEY WORDS

Bone, Osteoporosis, Biomarkers, Cell and Molecular imaging, Metabolic Bone Disease

INTRODUCTION

The cataloging of human mutations, the use of mouse genetics to recapitulate human disease, and the rapid evolution of methods in computational biology, including the ability to study the genome, transcriptome and cistrome, now at the single cell resolution, have together had a major impact on how basic biological research is translated into bedside medicine. Such has happened in bone biology with the discovery, through mouse genetics, of several medicines to treat osteoporosis and rare genetic diseases of bone. However, in achieving these strides, it has also become clear that the clinical question(s) that leads to purposeful biomedical investigation arises from the bedside. And, when the complexity of chronic diseases, such as osteoporosis, obesity and cancer, among others, has become challenging, one is prompted to resort to novel ways of examining hypotheses, studying pathophysiology, and unmasking therapeutic targets. Oftentimes to get true and meaningful answers to bedside–driven questions, one also

needs to break through silos, cross traditional disciplines, and use unfamiliar technologies – all of this contributes to collegiality and collaboration, with the ultimate goal of ensuring rigor and integrity of data so produced.

Figure 1 shows the collaborative hierarchy of what has been popularly termed as 'team science.' It starts from uni–disciplinarity, which relates to silos of interested scientists working independently, to multidisciplinary collaborations, where groups remain independent, but interact with others, generally in sequence and in response to specific needs. However, at a higher level, interdisciplinary collaborations represent true partnerships that are interactive and collaborative, whereas the very highest echelon of team science – transdisciplinarity – represents what generally evolves into an interdependent and highly interactive team of collaborators.

While there is an evolving interest in sociology of the science behind team science[1-4], we will focus here on our own lessons from both interdisciplinary and transdisciplinary teams, which have led us to extend our remit of interest from bone biology to obesity, cancer and rare genetic diseases. We used a progressively interdisciplinary model in which we included, at various steps, expertise from basic biochemistry to structural biology to clinical oncology. Using this format, we discovered that bisphosphonates – the most commonly utilized drugs for osteoporosis and skeletal metastasis, can be repurposed to inhibit the growth of certain cancers driven by the epidermal growth factor receptor (EGFR)[5; 6]. In a second longstanding effort to study the direct effects of pituitary hormones on bone[7-10], and more recently on adipose tissue and energy metabolism[11], we worked as a seamless team with Cliff Rosen's group and other collaborators, to not only utilize unfamiliar technologies, but also for others to replicate

and reproduce our joint data sets. Noting that new connections between bone and other tissues continue to be established[10], we share our own experience to provide bone biologists with practical ways of integrating bone with other tissues towards potential therapeutic advantages.

INTERDISCIPLINARY EFFORT TO RE–PURPOSE BISPHOSPHONATES FOR TREATING EGFR–DRIVEN CANCERS

Bisphosphonates have been the mainstay of the therapy for osteoporosis, where they have been conclusively demonstrated to reduce fracture risk[12]. Prior to the advent to this use, bisphosphonates were used widely for the treatment of bone diseases arising from cancer, including skeletal metastasis, hypercalcemia of malignancy and osteoporosis arising from cancer therapies[13]. The target cell for bisphosphonate action on bone is the osteoclast, under which the drug first sequesters and is then taken up into the cell by a yet uncharacterized mechanism. The drugs mainly act to inhibit the activation of a critical enzyme, farnesyl pyrophosphate synthase (FPPS), which is responsible for geranylgeranylation of GTPases to allow enzyme and acid secretion[14]. By inhibiting FPPS, bisphosphonates reduce bone resorptive activity of mature osteoclasts. Commonly utilized bisphosphonates, namely alendronate, risedronate, ibandronate and zoledronic acid, which have been shown to reduce the risk of fracture at various sites, display a rank order of potency in inhibiting FPPS *in vitro*[12; 14].

In addition to their prominent and well–documented skeletal actions, bisphosphonates have been shown to directly kill certain cancer cells and improve survival in people. The most compelling data sets arise in patients with breast and colon

cancers. Bisphosphonates utilized in early breast cancer without evidence of skeletal metastasis have been shown to reduce isolated tumor cell burden in bone marrow[15-17]. Furthermore, in patient subgroups in the ABSCG–12, ZO–FAST and AZURE breast cancer trials, zoledronic acid was found to significantly improved recurrence– and disease–free survival[18-20]. Furthermore, several epidemiologic studies have documented a reduced incidence of colon and breast cancer in women who are on bisphosphonate therapy for osteoporosis[21-23], and at least one study has shown a survival benefit in patients who remain on drug following their cancer diagnosis[21].

To us bone biologists, these sets of compelling studies with a bone–active drug posed the question whether bisphosphonates had additional actions on yet uncharacterized molecular targets, which could be the basis of their potential re–purposing as anti–cancer agents. We started with a team of two (M.Z. and L.S.), and recruited a colleague knowledgeable in genomics (J.I.), who helped us with an unbiased search for other potential targets using the recently developed connectivity map (C–MAP)[24]. This *in silico* tool, which connects genes, diseases and drugs, has now been extensively utilized to re–purpose 'old' drugs for new uses. Namely, the anticonvulsant topiramate is now being tested for inflammatory bowel disease[25], and trifuloperazine–like agents are being evaluated for the therapy of therapy–resistant, EGFR–driven non–small–cell lung cancers (NSCLC)[26]. We are also beginning, based on C–MAPping a gene signature from a mouse model of Gaucher disease, to evaluate two anti–schistosomal agents, which may bypass the effects of glucocerebrosidase deficiency in Gaucher disease[27].

With the inclusion of expertise in computation, we developed a bisphosphonate gene signature consisting of the most tightly associated genes with bisphosphonate action on the osteoclast, and interrogated C–MAP with this signature[5]. The top two hits were anti–cancer agents, 1,5–isoquinolinediol (a PARP inhibitor) and a first–generation EGFR inhibitor, AG–1478. In parallel, pathway analysis using KEGG highlighted associated pathways downstream of EGFR activation[5; 6]. This data set led to the next question – whether there is a relationship between bisphosphonates and cancers driven by EGFRs. This required expertise in oncology, and we therefore entered into collaboration with a cancer biologist (Dr. Goutham Narla, University of Michigan) and clinical oncologist (Dr. Matthew Galsky, Mount Sinai), to begin exploring potential uses for bisphosphonates in lung and breast cancers.

Lung cancer causes nearly a third of all cancer–related deaths worldwide estimated to be ~160,000 annually. A third of all NSCLCs are driven by activating mutations in the EGFR, prominently an L858R point mutation and a deletion mutation in exon 19 (Δ746–750). These mutations do not only cause unrestricted oncogenic signaling by allowing the Cα helix to collapse into the kinase domain, but also render the cancers sensitive to the two most commonly utilized first–line tyrosine kinase inhibitors, gefitinib and erlotinib[28]. However, with either agent, there is recurrence due to resistant mechanisms[29], about half of which have been attributed to a second–site mutation in the kinase domain, notably T790M[30].

With the assistance of our cancer collaborators, we could show that nitrogen–containing bisphosphonates (alendronate, ibandronate, risedronate, icandronate and zoledronic acid) caused apoptosis and cell cycle arrest in human NSCLC cell lines

bearing the respective EGFR mutations, namely H3255 (with the L858R mutation) and HCC827 (with the Δ746-750 deletion)[5; 6]. In contrast, the 'older' bisphosphonates that did not have an amino group (etidronate, clodronate, tiludronate and pamidronate) failed to kill cells – suggesting a structure–activity relationship, rather than a mass effect. Specifically, two agents zoledronic acid (used mainly in the US and Europe) and minodronic acid (used mainly in Asia), which had similar ring structures and two nitrogen atoms, displayed almost identical actions in reducing cell viability.

Exploration of the precise molecular mechanisms of action of bisphosphonates on EGFRs meant that we add a structural biologist to our team (S.H.). We hypothesized that, as bisphosphonates shared two phosphate groups with ATP, the molecules will likely bind with a weak affinity to the kinase domain of the EGFR[5; 6]. We performed computational modeling, including molecular dynamics and anisotropic network modeling, to establish that bisphosphonates could dock stably into the kinase domain of the EGFR. Using the crystal structure of the EGFR kinase domain, we found that zoledronic acid forms a bond *via* water with residue T790 of the EGFR and its imidazole ring docks into the adenine binding site. Through our collaboration with a biochemist (T.Y.), we developed a protein thermal shift assay to conclusively establish binding of bisphosphonates[6]. There was a clear shift in the melting temperature of recombinant EGFR in the presence of either bisphosphonate. Importantly, this thermal shift was abolished when the putative bisphosphonate–binding sites of EGFR were mutated by site–directed mutagenesis[5; 6]. We also explored signaling pathways downstream of the kinase pocket, and found that tyrosine phosphorylation of all downstream residues, together with associated signaling cascades, namely Stat3/5, Akt, NFκB and Erk1/2 were

attenuated substantially[5; 6]. A global reduction in EGFR signaling was consistent with the action of bisphosphonates at the kinase domain.

We studied whether bisphosphonates could synergize with erlotinib or gefitinib to mount a more profound effect on tumor cell viability. Through our continued structural biology collaboration, we were able to document, by computational modeling, that the two drugs together bound to the EGFR kinase domain, but with different binding modes than when each drug was docked on its own[5]. The concept that one 'big drug' could work better than two small drugs led to the testing of synergy both in colony–forming assays and xenotransplant studies. We found that bisphosphonates used together with erlotinib caused greater reductions in colony formation than each drug alone[5]. We also showed that while each drug inhibited tumor growth and caused apoptosis, the two drugs together resulted in profound tumor regression[5]. Of note is that EGFR–negative colon cancer cells, when similarly tested did not respond to bisphosphonate action, and that inhibiting EGFR expression in H3255 and HCC827 cells significantly attenuated bisphosphonate–induced cell killing, whereas inhibiting FPPS did not[5; 6] – this confirmed a primary action of bisphosphonates on cell viability *via* the EGFR.

We also explored whether bisphosphonates could be used in patients with the second site mutation, T790M. This mutation creates a steric clash with a nearby M766 residue in the L858R-T790M double mutant resulting in a 20° rigid rotation of the Cα helix so that erlotinib and gefitinib are unable to bind[5; 6]. However, the interaction with bisphosphonates is preserved, testified by the robust inhibition of cell viability in a cell line that harbored both the driver (L858R) and resistance (T790M) mutations.

These findings together suggest that the widely–utilized bone–active bisphosphonates could potentially be repurposed as anti–cancer agents for tumors that are driven primarily by either overexpression or constitutive activation of the EGFR family of receptors, such as NSCLC, breast, colon, gastric, and head and neck cancers. From our combination therapy dataset, it seems possible that bisphosphonates could become valuable adjunctive therapies for patients on tyrosine kinase inhibitors, particularly in cases of resistant disease, where patients follow a downhill course. Furthermore, our prevention model documents robust effects of bisphosphonates on HER2–driven breast cancer[5]. And finally, having teamed up with a medicinal chemist (Dr. Michael Ohlmeyer, Mount Sinai), we are designing a new class of drugs, which we predict are as, if not more, potent that the current tyrosine kinase inhibitors, and may also overcome the early resistance. Our 'farm approach' for interdisciplinary collaboration developed as key questions arose (Figure 2) appeared therefore to deliver a strong platform for re–purposing a common class of drugs for important therapeutic uses.

TRANSDISCIPLINARY EFFORTS LEAD TO THE DISCOVERY OF FSH ACTION ON BONE AND FAT

In 2003, we provided the first evidence that pituitary hormones, otherwise thought to have unitary associations with target tissues, could act directly on the skeleton through G–protein–coupled receptors[7]. Notably, shortly after discovery of neural circuits for the regulation of bone mass through the sympathetic nervous system[31], we found that both thyroid-stimulating hormone (TSH) and follicle-stimulating hormone (FSH), thought solely to regulate thyroxine secretion from the thyroid gland and ovarian estrogen production, respectively, could act on osteoclasts to regulate bone resorption[7; 8]. Since

then not only has every pituitary hormone, namely FSH, TSH, growth hormone, adenocorticotrophic hormone (ACTH) and prolactin, as well as posterior pituitary neuropeptides, oxytocin and vasopressin, been shown to act directly on bone, but also that certain of these hormones are produced by bone cells to exert potential autocrine and paracrine actions[7-10; 32-39]. Subsequently, clinical associations between pituitary hormones and bone, body composition, and energy metabolism have been documented using various cohorts across the globe [reviews: Refs 9; 40].

Collectively, these studies have not only yielded new insights into integrative physiology specifying a pituitary–bone axis and pituitary–metabolic circuits of medical significance, but have also led to efforts at remapping single–hormone hypotheses for the pathophysiology of human osteoporosis. Thus, it is becoming increasingly accepted that the osteoporosis of hyperthyroidism and hypogonadism, which was solely attributed to changes in thyroxine and estrogen levels, also have contributions from reduced TSH and elevated FSH levels respectively[9; 40]. Likewise, the osteoporosis of pregnancy and lactation and that resulting from chronic hypernatremia are being attributed to increased levels of oxytocin and vasopressin[9; 40]. Here, we will focus on the role of FSH in causing bone loss and adiposity – studies that were performed and validated in a truly transdisciplinary manner and have formed the framework for the development of an anti–FSH antibody as a potential therapeutic for both osteoporosis and obesity.

Indeed, it is clear from the Study of Women's Health Across the Nation (SWAN) that women entering menopause display an accelerated phase of bone loss, with ~50% of bone loss occurring within the first 5 years of menopause. This is accompanied by the onset of visceral obesity, disrupted energy homeostasis, and reduced physical activity in

millions of women worldwide[41-48]. The bone loss has been attributed solely to estrogen deficiency since the time Fuller Albright described post–menopausal osteoporosis[49]. However, a more careful look at the SWAN data indicates that the most rapid rates of bone loss occur ~3 years prior to the onset of the last menstrual period[47; 48]. During this period in a woman's life (between 42 and 54 years), irrespective of ethnicity, estrogen levels are relatively normal while FSH levels are rising[41]. We therefore surmised that the rapid rates of bone loss cannot be attributed to hypoestrogenemia and that elevated FSH levels may play a causal role.

We found FSH receptors (FSHRs) on osteoclasts from various species, including human CD14-derived cells, which were coupled to a $G\alpha_{i2}$ protein (instead of coupling to a $G\alpha_s$ protein in ovarian follicular cells)[8; 50; 51]. Activation of the FSHR resulted in increased formation, activity and survival of osteoclast by synergizing the MAP kinase, Akt and NFκB pathways[8]. Furthermore, we separated the potentially confounding effects of estrogen from the pro–resorptive actions of FSH using mice lacking FSHβ[8]. Specifically, mice haploinsufficient in FSHβ, namely *Fshb*^{+/-} mice, showed no evidence of ovarian dysfunction, whereas there was a significant increase in bone mass due to suppressed osteoclastic bone removal[8]. Collectively, the data documented a direct action of FSH to increase the resorption of bone, leading to the hypothesis that some of the bone loss seen in the late perimenopause could arise from elevated serum FSH in the face of normal estrogen levels[41; 46]. The question was whether blocking the action of FSH during this period would prevent postmenopausal bone loss.

These initial observations led us to our structural biology collaborator, who used the crystal structure of the human FSHR–FSHβ complex to model and fine map the

equivalent mouse complex[52; 53]. This led us to use a 13–amino–acid–long sequence of FSHβ as the target for our initial antibody. Our approach for using a highly–targeted antibody to the ligand had several advantages. First, one could titrate antibody levels so as to spare the ovaries by leaving enough circulating FSH unblocked. Second, the human and mouse peptide sequences differed in just two amino acids, so that even a humanized antibody would likely recognize mouse FSH, thus enabling its future testing in mouse models. Third, blocking the FSHR-binding domain of FSHβ using a large immunoglobulin molecule is likely to prevent FSH access into the small binding pocket of the FSHR[52]. Thus, our polyclonal antibody reduced the fall of bone density that was triggered upon ovariectomy in mice[53; 54], providing proof–of–concept for a potential therapeutic use in postmenopausal osteoporosis. We also noted that the antibody not only inhibited bone resorption in these ovariectomized mice, but surprisingly also stimulated bone formation[52; 53]. Noting that we did not find FSHRs on mature osteoblasts, we documented expression of these receptors on mesenchymal stem cells[53], which are also precursors for adipocytes. We therefore questioned, on the basis of preliminary data that, if an anti–FSH antibody was pro–osteoblastic, could it also possess anti–adipocytic actions?

The anti–FSH antibody did indeed reduce body fat on dual energy X–ray absorptiometry (DXA), in addition to increasing bone mass[11]. This dataset became the beginning of a 5–year–long, highly productive and mutually–rewarding transdisciplinary collaboration with Dr. Clifford Rosen – we jointly asked the question whether our anti–FSH antibody could build bone and reduce body fat. In doing so, key data sets were replicated in Dr. Rosen's lab using either the same or different technologies[11; 55]. We each

found that following ovariectomy or after being fed with a high–fat diet, mice receiving the anti–FSH antibody lost body fat, and that this was independent of food intake that was somewhat increased[11]. Both our groups used DXA, quantitative NMR and direct weight measurements to document these effects in both male and female mice of different ages[11]. The need for further confirmation, particularly as both our groups were beginning to tread into a new field of obesity and metabolism, was to have the fundamental premise validated, and we did so by including Dr. X. Edward Guo (Columbia University), who replicated our data set using micro–CT imaging. He found a dramatic reduction in fat mass in the visceral and subcutaneous compartments of antibody–treated mice, and further, that this effect phenocopied the effect of *Fshr* haploinsufficiency[11]. Overall, this triple validation strategy of key data through an extended collaboration provided the most robust evidence for an anti–adiposity action of our FSH antibody. Please refer to of our *Nature* paper, which attributes each experiment to a given principal investigator in order to ensure transparency[11].

We also established specificity of FSH blockade through a collaboration with Dr. Henrik Molina at the Rockefeller University Proteomics Resource Center. Mass spectrometry documented FSH in eluates from anti–FSH–antibody–immobilized columns[11]. Blocking action was confirmed using ThermoCells that report the activation of uncoupling protein 1 (UCP1), a mitochondrial protein involved in thermogenesis. Pharmacokinetic studies in mice documenting high enough antibody concentration in the serum provided further validation. The presence of FSHRs on adipocytes, *albeit* at an 8–fold lower level than the ovaries, was confirmed complementarily by quantitative PCR, Sanger sequencing of the full length receptors from primary adipocytes and 3T3.L1 cells,

and functional assays on regulation of downstream gene program[11]. We also collaborated with Dr. Aaron Hsueh (Stanford University), as part of our transdisciplinary approached. His group established, using a fluorescently–labeled FSH molecule FSH–CH, *in vivo* FSH binding to adipose tissue that was displaceable by unlabeled FSH[52]. We further found that FSH inhibited the β3 adrenergic signaling pathway, and that the FSHR was coupled (as in bone) to a pertussis–toxin–sensitive $G\alpha_i$[11]. Xenotransplant studies, wherein ThermoCells were injected into nude mice, revealed marked increases in UCP1 expression *in vivo*, thus suggesting that the FSH pathway was anti–thermogenic[11]. Blocking FSH with our antibody thus induced thermogenic adipose tissue *in vivo*[11].

To be scientifically meaningful, studies needed not only to be repeated and reproduced in other labs (that we heavily relied upon), but also to be replicated using other technologies. To study the induction of thermogenic adipose tissue, we utilized complementary technologies at various labs. At Mount Sinai, we injected ThermoMice, which express *Luc2/tdTomato* driven by the *Ucp1* promoter, with antibody and used the IVIS platform to assess luminescence *in vivo* – strong signals were seen in areas with predominantly brown or white adipose tissue[11]. This suggested not only brown fat activation, but also the conversion of white adipose tissue to energy–producing beige adipose tissue. Experiments with ThermoMice were replicated in Cliff Rosen's lab under thermo–neutral conditions. Second, white–to–beige transition (or 'beiging') induced by our anti–FSH antibody given to mice on a high-fat diet was further explored using traditional immunocytochemistry for UCP1, as well as by quantitative PCR for a host of brown fat genes, such as *Ucp1*, *Cidea*, *Cox7a* and *Cox8*, that were all elevated in white fat[11]. Third, as beiging is associated with increased mitochondrial bioenergetics, we used

the PhAM mouse, which reports mitochondria. We documented marked increases in mitochondrial density in all fat depots[11]. Furthermore, to study metabolic effects, Cliff Rosen performed indirect calorimetry on mice on a high-fat diet that were treated with anti–FSH antibody. This study confirmed increases in energy expenditure and oxygen utilization, but with evidence for increased physical activity[11]. Finally, to determine whether the enhanced physical activity noted with our antibody contributed to increased energy expenditure, we collaborated with Dr. Jan van Klinken (University of Leiden), a biomathematician and an expert in analyzing metabolic cage data. The raw dataset from metabolic cages was analyzed rigorously using penalized spline regression, which allows the separation of basal and physical–activity–induced increases in metabolic rate. We found, through this important collaboration, that the increased energy expenditure induced with the anti–FSH antibody was occurring independently of physical activity, and likely arose from beiging and brown adipose tissue activation.

In summary, we have found through an extensively validated set of data that FSH inhibition stimulates bone formation, inhibits bone resorption, reduces body fat and converts white adipose tissue to thermogenic 'beige' adipose tissue. Our transdisciplinary collaborative program, besides providing valuable expertise in areas beyond our own breadth, also represents our investigative team's profound effort towards ensuring rigor. It provides an example of exceptional level of transparency – free exchange of reagents, raw data sets, Excel spreadsheets, and cross–confirmation at all levels. Candid discussions about reproducibility and replicability led to consensus data being submitted for publication. We term this "contemporaneous replication" – a level of rigor that, we believe, contributed to our recent NIH U19 funding[11; 55].

As noted above, there is clear evidence that osteoporosis and obesity track together at menopause. Furthermore, there is an evolving consensus that obesity itself may predispose to bone loss. However, the potential clinical application of our findings is based on recent compelling human evidence from a urology group in Denmark. Østergren *et al.* asked the question whether FSH contributes to human obesity. In an interventional clinical trial, wherein 58 treatment–naïve prostate cancer patients underwent subcapsular orchiectomy or were given a GnRH analog triptorelin, in both instances to reduce testosterone levels to near–zero[56]. Notably, orchiectomized patients with high FSH and LH levels had a higher body weight, total fat mass, and subcutaneous adipose tissue, with a trend towards higher visceral adipose tissue[56]. This study lays down the firm basis for the potential for an anti–FSH therapy for obese people. Towards this, we have developed monoclonal antibodies to the human and mouse FSHβ sequences. These antibodies have now been humanized and await affinity maturation before entering the commercialization pipeline.

OUR LESSONS

Being involved for the past decade in what is now popularly termed 'team science'– both interdisciplinary and transdisciplinary – we find that the whole has always been greater than the sum of the parts. We initially laid out the framework of our focus on groundbreaking research that served as the fundamental catalyst in the development of our collaborations. We discovered that in establishing a multidisciplinary scientific team, where individuals share collective identity, are interdependent and mutually committed to the project, and take shared accountability for the outcome, the most important attribute was team "synergy". This synergy allowed each entity to come together and glean the

necessary intellectual capital needed – building on and expanding strengths, while simultaneously overcoming or filling gaps and perceived weaknesses. Team development requires personal and collective maturity and internal acceptance of the fact that, in order to achieve scientific breakthroughs, we need to operate above and beyond our personal egos and ambitions. It takes time, trust, mutual respect, and a collective vision.

In building our team, we faced and addressed challenges. The average timeframe to complete an NIH-funded project is 3-5 years. However, the formation of a mature team can take a few years. Therefore, a team may sometimes operate at full capacity only 2/3 of the allocated time. The individualistic culture in academic medicine focuses on the perceived "independence" of individual investigators, and seems to perpetuate the fear that more than one member of the team will be credited for their work. Multicultural and transgenerational scientific environments are associated with complicated communication styles due to differing backgrounds and a tendency to stereotype. While moving from self-identity to group identity and from independence to interdependence, ongoing issues of status, power and autonomy can be distractors and must be managed thoughtfully. Therefore, while some would state "*I make a pretty good team*," others might say that "*sometimes I think that the collaborative process would work better without you*."

There is no single universal solution as to how to overcome these barriers; however, we found that it was crucially important to keep the team focused on their role in the "big picture". We found that by maintaining transparency, delineating and continuously reaffirming roles and responsibilities by being open through frequent communication, we could be successful. These tenets have helped build trust and lasting

relationships with our collaborators, with an added benefit of ensuring rigor and integrity of our datasets.

Notably, for us the gain of new knowledge and evolution of its therapeutic implications have been profound. Biologically, it has allowed out–of–the–box concepts to emerge and mature – and this has led to novel testable hypotheses, such as the concept of pituitary–metabolic circuitry. It has also allowed, and importantly encouraged, diversification of our interests – from bone biology to obesity, metabolism, and cancer. Moreover, our 'team science' resulted in the submission and subsequent award of a U19 application, supported by National Institute of Aging (NIA). This opportunity has allowed us for the smooth transition needed to foster scientific independence of three of our younger principal investigators – namely, T.Y., J.I. and D.L.

As we are facing the emerging changes in contemporary science, including globalization and greater advances in technology, it is crucial for NIH and academic institutions to provide more support for the integrative 'team science' approach. It is our hope that interdisciplinary and transdisciplinary collaborations will continue to expand the scope of bone biology research to a much more provocative organismal front.

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LEGENDS TO FIGURES

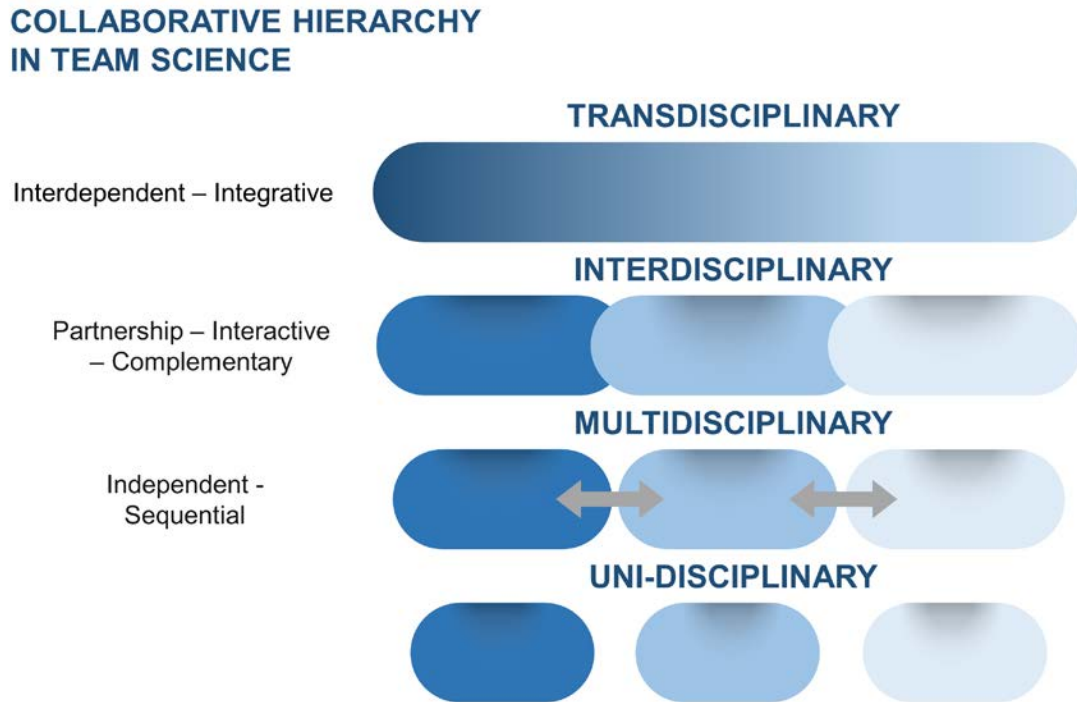**Figure 1:** Collaborative Hierarchy of Team Science.

Figure 2: Interdisciplinary Approach for Repurposing Bisphosphonates for Cancer Therapy.