2023 IBM Research review
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Synopsis: For me, 2023 was a frustrating year in the research on IBM. There was no consensus on the nature of the disease or an approach to treatment. On the other hand, we learned a lot.

One theme emerging from the literature suggests that inclusion body myositis is one disease but with several different sub-types — think of it like a tree that has several different branches. Although they are all IBM at their root, each branch — sub-type — may exhibit important differences. The idea of IBM as a spectrum disorder was introduced (Kleefeld et al., 2022). What does this mean for IBM? IBM can be seen as a group of sub-types that exhibit a range (a continuum or spectrum) of different symptoms, severity, and characteristics. For example, we now appreciate differences in IBM in black patients and female patients that seem to represent discrete subgroups, implying diverse trajectories and potentially different responses to treatment. Also, Taira highlighted three clinical subgroups based on the presentation of IBM in the arm, leg, or swallowing difficulties. The idea of a type of IBM that is an early onset subtype was introduced, with this group showing a mean age of onset of 38 and a mean age at diagnosis of 45. Polymyositis appearing with mitochondrial abnormalities (PM-Mito) likely reflects an early presentation of IBM, at least in many cases. The two can be differentiated by looking at cytotoxic T cells — IBM has them, PM-Mito does not. Finally, a type of IBM is associated with HIV. HIV-IBM can be differentiated based on the presence of cytotoxic T cells showing KLRG1. It would be interesting to look at each subtype and see if there are variations at the genetic level. See table.

The need for better measurements of weakness, specifically aimed at IBM, was seen. Accurately measuring weakness is very important in establishing the effectiveness of treatments. Using a strategy based on muscle endurance (for example, grip strength tests or repeated walking tests) may be better than manual testing (for example, when the doctor has you press your knee up against their hand).

Looking at swallowing difficulties, it was noted that more research needs to be done on treatments and that swallowing difficulties, along with respiration, need to be monitored and managed on an ongoing basis.

Exercise: it was always believed that exercise required working muscles hard, but it was found that restricting blood flow during low-impact exercise is effective. Longer daily rehabilitation may result in better improvements. Adding testosterone during exercise does not improve strength.

The role of the anti-NT5c1A antibody in IBM remains unclear. There seem to be no differences between patients who have the anti-NT5c1A antibody versus those who do not.

A potentially new marker for IBM in the urine has been discovered and looks promising. If two chemicals are both detected in the urine, this shows 100% sensitivity and specificity for IBM. Obviously, more research will be done on this as a diagnostic tool.

The first clinical trial against an immunological target in IBM (KLRG1), organized by the ABCURO company, is underway, and we should learn a lot from it.
Speculation of IBM as a spectrum disease (IBM-SD) (see Kleefeld et al., 2022)

<table>
<thead>
<tr>
<th>Sub-type</th>
<th>Characteristic</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Familial IBM (fIBM)</td>
<td>IBM in two or more patients within a single generation in a family.</td>
<td>See Ranque-Francois et al., 2005</td>
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<tr>
<td>early-onset IBM</td>
<td>mean age at symptom onset 38 and mean age at diagnosis 45</td>
<td>Lindgren et al., 2023</td>
</tr>
<tr>
<td>“Normal onset” IBM</td>
<td>mean age at symptom onset 64 and mean age at diagnosis 70</td>
<td></td>
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<tr>
<td>“Normal” IBM</td>
<td>Moderate to severe (Disabling) weakness</td>
<td>Anecdotal evidence</td>
</tr>
<tr>
<td>“Mild” IBM</td>
<td>Mild to moderate weakness – Slower progression?</td>
<td></td>
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<tr>
<td>IBM in Black patients</td>
<td>differences in pattern and progression of weakness</td>
<td>Michelle et al., 2023</td>
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<tr>
<td>IBM in females</td>
<td>differences in pattern and progression of weakness</td>
<td></td>
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<tr>
<td>NT5C1A positive</td>
<td>??? Implications unclear</td>
<td>See e.g., Lee et al., 2023</td>
</tr>
<tr>
<td>NT5C1A negative</td>
<td>??? Implications unclear</td>
<td></td>
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<tr>
<td>“Arm subtype”</td>
<td>higher IntraMAT content of proximal arm muscles; supraspinatus, deltoid, infraspinatus, subscapularis, biceps, and triceps</td>
<td>Taira et al., 2023</td>
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<tr>
<td>“Leg subtype”</td>
<td>IntraMAT content mainly in quadriceps muscles</td>
<td></td>
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<tr>
<td>“Dysphagia subtype”</td>
<td>cricopharyngeal bar</td>
<td></td>
</tr>
<tr>
<td>HIV-IBM</td>
<td>no KLRG1+ or CD57+ cells</td>
<td>Vogt et al., 2023</td>
</tr>
<tr>
<td>PM-Mito</td>
<td>Early form of IBM?? [“early IBM”]</td>
<td>See Kleefeld et al., 2023; Lacomis, 2023; Tanboon et al., 2023</td>
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<tr>
<td>HLA-DRB1*03:01:01</td>
<td>Alters the DRβ1 protein. With an under-representation of DRB4<em>01:01:01 and DA1</em>01:02:01 leads to a 14X higher risk of IBM</td>
<td>Slater et al., 2023</td>
</tr>
<tr>
<td>Level of mitochondrial DNA mutation load</td>
<td>severity of mitochondrial damage is strongly associated with the degree of inflammation and muscle fibre atrophy; disease-related fatigue and exertion mitochondrial impairment</td>
<td>De Paepe, 2019; Joshi et al., 2014; Lindgren et al., 2023; Nagy et al., 2023</td>
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</tbody>
</table>

The best treatment for IBM today: closely monitoring swallowing and respiratory function, creating an individualized exercise routine and addressing mobility using aids to prevent falls and injuries.

Selected articles:

Michelle: Among the 335 patients meeting inclusion criteria for IBM, 64% were male with an average age of disease onset of 58.7 years and delay to diagnosis of 5.2 years. Initial misdiagnosis (52%) and immunosuppressant treatment (42%) were common. Less than half (43%) of muscle biopsies demonstrated all three pathologic hallmarks: endomysial inflammation, mononuclear cell invasion, and rimmed vacuoles. Black patients had significantly weaker arm abductors, hip flexors, and knee flexors compared to non-Black patients. Female patients had stronger finger flexors and knee extensors compared to their male counterparts. Younger age (less than 50 years) at onset was not associated with increased weakness. … These findings suggest that Black and female
patients represent clinically distinct subgroups within IBM with unique disease trajectories and, potentially, different responses to therapeutic interventions. The origin of these differences in clinical phenotype and disease progression are unclear.

Roy: There are inconsistencies in using outcome measures in clinical studies in IBM. The core set measures developed by the IMACS group for other IIMs are not directly applicable to IBM. As a result, there is an unmet need for an IBM-specific core set of measures to facilitate the evaluation of new potential therapeutics for IBM.

Leclair: This scoping review of 33 studies reporting on pain measures in AIM indicates that the burden of pain in subjects with AIM is greater than that of the general population and comparable to other chronic rheumatic diseases such as rheumatoid arthritis.

Cantó-Santos: These findings confirm the presence of molecular disturbances in peripheral tissues from IBM patients and prompt patients' derived fibroblasts as a promising disease model, which may eventually be exported to other neuromuscular disorders. We additionally identify new molecular players in IBM associated with disease progression, setting the path to deepen in disease aetiology, in the identification of novel biomarkers or in the standardization of biomimetic platforms to assay new therapeutic strategies for preclinical studies. … in the present study we validated fibroblasts as a disease model for IBM, showing IBM alterations are present beyond the target tissue of the disease. This model could be exported to other myositis or neuromuscular diseases. Additionally, we unveil numerous pathways and specific molecules that emerge as relevant key players in disease aetiology or evolution, for further evaluation as candidate biomarkers or therapeutic targets.

Mitra: The role of myostatin is crucial in determining muscle homeostasis, as talked about throughout the article. It is an essential signalling molecule/myokine that dictates the fine balance between protein degradation and synthesis in skeletal muscles. Furthermore, the role of myostatin is not only restricted to muscles but can also be extrapolated to the bones as well. Hence, developing therapeutic interventions to target myostatin can be useful for tackling both muscle wastage disorders as well as inflammatory diseases of the bones.

Tani: The results show that a longer daily duration of rehabilitation results in improved activities of daily living for inpatients with sporadic inclusion body myositis.

Ma: IBM increases a patient's risk for dysphagia, falls, and infection as compared to other IIM patients.

Lee: Clinically significant differences were not found between anti-NT5c1A antibody-seropositive and seronegative IBM groups with respect to gender, age at symptom onset, age at diagnosis, disease duration, serum CK values, presence of other autoantibodies, dysphagia, and the pattern of muscle impairment.

Connor: Adding testosterone supplementation to exercise training did not significantly improve muscle strength or physical function over a 12-week intervention period, compared to exercise alone. However, the combination improved emotional well-being over this period, and relative stabilisation of disease was found during the 12-month OLE. A longer duration trial involving a larger group of participants is warranted.

Shaik: IBM is the leading cause of debilitating dysphagia related to inflammatory myopathies and is most common in those over the age of 50. The prevalence of dysphagia is estimated to be 50% per the Euro myositis registry, 56% per meta-analysis, and 40% per retrospective study. Up to 80% of participants reported symptoms when a targeted questionnaire seeking symptoms of dysphagia was performed in a cohort with IBM. About 10% may present with dysphagia as an isolated clinical feature. For instance, Shibata et al. describe a case report in which a patient with IBM had dysphagia for five years prior to the onset of limb muscle weakness. Dysphagia usually presents at an advanced disease stage, resulting in unsatisfactory treatment outcomes.
Ambrocio: Dysphagia is a common debilitating clinical feature of IBM. However, the impact of dysphagia in IBM has been historically overlooked. This study aimed to identify, evaluate and summarize the evidence regarding the assessment and management of dysphagia in persons with IBM undergoing treatment. ... Conclusion: Various interventions have been reported to temporarily improve dysphagia in persons with IBM. However, these findings are based on limited and overall low-quality evidence. This study cautions against the generalization of these findings and emphasizes the need for further systematic research to improve the diagnosis and management of dysphagia in IBM.

Cantó-Santos, Integrated multi-omics analysis: we aimed to identify novel target molecules and pathways in IBM that may prove to be non-invasive biomarkers, focusing on the mitochondrial and metabolic profile of the disease, by performing an omics analysis (targeted metabolome and RNA seq analyses) of different biological samples isolated from IBM patients (saliva, urine, plasma, fibroblasts, and muscle). ... The sensitivity and specificity values are 50.0% and 83.3% for L-pyroglutamic acid and 100.0% and 83.3% for orotic acid, but these values changed to 100% sensitivity and specificity when both acids were tested together. The presence of altered organic acids in urine corroborated the imbalanced organic acid profile in fibroblasts and highlights L-pyroglutamic and orotic acid as potential fluid biomarkers. ... All these multi-omics and interactome connections between metabolites and genes confirm the impact of metabolic dysregulation in IBM. ... When the organic acid profile was examined in the subjects' urine and more metabolites were detected, L-pyroglutamic acid and orotic acid emerged as a surrogate biomarker of this disease. ... – Metabolic dysregulation in IBM is present outside the target tissue (muscle), as seen in the altered organic acids in fibroblasts and urine; ... – The multi-omics profiling of patients’ samples allows for the evaluation of disease-associated phenotypes, constituting an untargeted approach enabling the potential detection of novel molecular players; ... – The detection of L-pyroglutamic and orotic acids in urine displayed an outstanding biomarker signature, with 100% sensitivity and specificity; ... – The validation of potential biomarkers in non-invasive samples like urine may eventually aid in the screening of patients' disease progression and treatment efficacy.

Taira: This study indicates the clinical subsets of IBM to expand the knowledge of the heterogeneity of the patients.

One subgroup (n = 18; proximal arm type) corresponded to patients with higher IntraMAT content of proximal arm muscles; supraspinatus (32.7 ± 4.3%, p < 0.01), deltoid (28.5 ± 4.4%, p < 0.01), infraspinatus (28.6 ± 3.9%, p < 0.001), subscapularis (37.4 ± 4.7%, p < 0.01), biceps (31.0 ± 3.5%, p < 0.001), and triceps (47.8 ± 5.1%, p < 0.001).

The second subgroup (n = 11; upper leg type) corresponded to patients involving IntraMAT content mainly in quadriceps muscles.

The third subgroup (n = 16; dysphagic type) corresponded to patients with dysphagia having cricopharyngeal bar (100%, p < 0.001), high SDQ scores (16.8 ± 2.3, p < 0.001), less IntraMAT content of rectus femoris (1.4 ± 0.7%, p < 0.01), vastus lateralis (23.5 ± 6.6%, p < 0.05), vastus intermedius (13.9 ± 4.7%, p < 0.05), vastus medialis 2/2 (9.5 ± 3.7%, p < 0.01), supraspinatus (12.4 ± 3.5%, p < 0.01), deltoid (5.5 ± 1.4%, p < 0.001), infraspinatus (7.6 ± 2.1%, p < 0.001), subscapularis (11.6 ± 3.9%, p < 0.01), biceps (6.6 ± 1.8%, p < 0.001), and triceps (13.1 ± 3.0%, p < 0.001).

Skolka: Current management approach for IBM consists of close monitoring of swallowing and respiratory function, adapting an exercise routine, and addressing mobility issues.

Garand: Recent investigations confirm that dysphagia in IBM is a debilitating and complex symptom that warrants timely evaluation and management. Further, they highlight the lack of validation of standardized swallowing-related metrics specifically for IBM and the limited evidence supporting a consensus of management ap-
proaches. Small scale research and clinical anecdotal data support a multidisciplinary and multipronged patient-centered approach, including rehabilitative exercise protocols, for dysphagia management in IBM.

Machado: Arimoclomol did not improve efficacy outcomes, relative to placebo, but had an acceptable safety profile in individuals with inclusion body myositis. This is one of the largest trials done in people with inclusion body myositis, providing data on disease progression that might be used for subsequent clinical trial design.

Vogt: Despite HIV-IBM and sIBM sharing important clinical, histopathological, and transcriptomic signatures, the presence of KLRG1 cells discriminated sIBM from HIV-IBM. This may be explained by longer disease duration and subsequent T-cell stimulation in sIBM. Thus, the presence of TEMRA cells is characteristic for sIBM, but not a prerequisite for the development of IBM in HIV+ patients. … Based on molecular data, the concept of an IBM spectrum disease (IBM-SD) has recently been introduced. IBM-SD describes the clinical and histomorphological spectrum ranging from mild inflammation and mitochondrial abnormalities to full-blown IBM.

Lindgren: In a population-based study during a 33-year period, 142 patients with IBM were identified in western Sweden. Six patients fell outside the inclusion criteria due to young age at symptom onset and had a first muscle biopsy less than 50 years of age. These were designated as early-onset IBM and included in this study. … The mean age at symptom onset was 38 years and mean age at diagnosis was 45 years in patients with early-onset IBM, while mean age at symptom onset was 64 years and mean age at diagnosis was 70 years in the corresponding IBM cohort. Four patients with early-onset IBM were deceased at a mean age of 61 years, compared with a mean age of 80 years at death in the corresponding 73 deceased patients with IBM. The mean survival from diagnosis was 14 years. Five patients had swallowing difficulties. The mean decline in quadriceps strength per month was $1.21\pm0.2$ Newton, corresponding to $0.91\pm0.2\%$. The remaining strength correlated to time from diagnosis ($p$ less than 0.001). Mitochondrial changes including cytochrome c oxidase deficiency were a consistent finding in the muscle biopsies. Despite their young age, patients had a high mitochondrial DNA mutation load in muscle tissue compared to age-matched controls. Early-onset IBM is a severe inflammatory myopathy, causing progressive muscle weakness, high mitochondrial DNA mutation load in muscle fibers and a reduced cumulative survival in young and middle-aged individuals.

Nelke: Fibro-adipogenic progenitors (FAPs) are a mesenchymal cell population with high phenotypical plasticity that is crucially involved in skeletal muscle homeostasis and regeneration. Here, we report that tissue-resident FAPs, not myofibers, are the main cell type assuming a senescent phenotype in IBM. Depending on environmental cues, FAPs may differentiate into fibroblasts or adipocytes. In response to muscle damage, FAPs proliferate, expand and accumulate, constituting the main source of extracellular matrix proteins. Depletion of FAPs hinders muscle repair underscoring their functional importance. Conversely, in conditions of chronic muscle damage, FAPs may prove detrimental to muscle health. Their persistent activity cumulates in progressive tissue fibrosis and loss of normal tissue architecture. In line, we describe a novel population of senescent FAPs that reside in IBM muscle. These FAPs exhibit key hallmarks of cellular senescence, including a pro-inflammatory secretome, engagement of the Jun/JunB-pathway and expression of senescence biomarkers (p21 and SA-β-Gal).

Suzuki: The presence of DEGs in sIBM suggests that the myotubes formed from sIBM-derived myoblasts revealed the existence of muscle cell-autonomous degeneration in sIBM. The catalogue of DEGs will be an important resource for future studies on the pathogenesis of sIBM focusing on primary muscle degeneration.

Chen: This review aims to provide a comprehensive overview of the role of the gut microbiota in muscle atrophy-related diseases. We summarize clinical and pre-clinical studies that investigate the potential for gut microbiota modulation to enhance muscle performance and promote disease recovery. Furthermore, we delve into the intricate interplay between the gut microbiota and muscle atrophy-related diseases, drawing from an array of studies. Emerging evidence suggests significant differences in gut microbiota composition in individuals with muscle atrophy-related diseases compared with healthy individuals. It is conceivable that these alterations in the
microbiota contribute to the pathogenesis of these disorders through bacterium-related metabolites or inflammatory signals. Additionally, interventions targeting the gut microbiota have demonstrated promising results for mitigating disease progression in animal models, underscoring the therapeutic potential of modulating the gut microbiota in these conditions. By analyzing the available literature, this review sheds light on the involvement of the gut microbiota in muscle atrophy-related diseases. The findings contribute to our understanding of the underlying mechanisms and open avenues for development of novel therapeutic strategies targeting the gut-muscle axis.

Winkler: Our high-level microbiome analysis did reveal significant differences of the gut microbiome in patients only for older: Pects, indicating that a more refined analysis may be needed. Cause effect relationships are notoriously difficult to determine for microbiome changes in diseases, and our sIBM findings are no exception to this.

Di Leo: mitochondrial dysfunction in skeletal muscle fibres occurs with both healthy aging and a range of neuromuscular diseases. The impact of mitochondrial dysfunction in skeletal muscle and the way muscle fibres adapt to this dysfunction is important to understand disease mechanisms and to develop therapeutic interventions. Furthermore, interactions between mitochondrial dysfunction and skeletal muscle biology, in mitochondrial myopathy, likely have important implications for normal muscle function and physiology. In this review, we will try to give an overview of what is known to date about these interactions including metabolic remodelling, mitochondrial morphology, mitochondrial turnover, cellular processes and muscle cell structure and function. Each of these topics is at a different stage of understanding, with some being well researched and understood, and others in their infancy. Furthermore, some of what we know comes from disease models. Whilst some findings are confirmed in humans, where this is not yet the case, we must be cautious in interpreting findings in the context of human muscle and disease. Here, our goal is to discuss what is known, highlight what is unknown and give a perspective on the future direction of research in this area.

Behringer: For a long time, it was firmly believed that a high load in strength training was necessary to achieve muscle mass and strength gains. However, blood flow restriction training has fundamentally challenged this assumption. Numerous studies over the past decades have shown that these biopositive effects can be achieved even with low loads when blood flow to the working muscles is restricted and venous return from the working extremity to the heart is interrupted… A total of 35 experts participated in this Research Topic and presented the results from their current investigations. A total of nine studies were accepted to be published in the Research Topic. … The studies in this Research Topic have demonstrated that BFR training can be used successfully in a variety of clinical settings.

Amici: Muscle endurance testing may identify muscle impairment inadequately described by manual muscle testing (MMT), particularly in patients with high MMT scores.

Tanboon: PM with mitochondrial pathology (PM-Mito), which contains features resembling IBM except for rimmed vacuoles (i.e., endomysial inflammation, mitochondrial pathology, highly differentiated cytotoxic T cells, and type 2 interferon [IFN2, IFN-Y] pathway upregulation) has been re-recognized and proposed as early IBM (eIBM) in IBM-spectrum disease… Notably, GBP6 IHC positivity in a muscle biopsy containing highly differentiated cytotoxic T cells (highlighted by KLRG1, CD57, and PD1 expression) differentiates IBM from PM-Mito

McLeish: Altogether, these results suggest that T-LGL expansion occurring in IBM patients is correlated with exacerbated immune dysregulation and increased disease burden.
Lacomis: Kleefield et al recently provided more evidence that there are dysfunctional T cells in IBM, a possible clue to the treatment resistant state. … The investigators feel that PM-Mito is an early form of IBM. They concluded that “specific IFN-mediated inflammation plays a key role in both IBM and PM-Mito.”

Argyriou: This study shows that T cells in skeletal muscle of patients with IIM display tissue resident memory features suggesting their maintenance within the tissue and their probable contribution to relapses. The immunoprofiling map of muscle-infiltrating T cells can be used to understand the mechanisms leading to tissue damage and to identify novel therapeutic targets.

Other references
