Immunity and Immunopathogenesis of TB

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Most individuals infected with *MTB* do not develop active disease

- **MTB Exposure**
  - Not infected
  - 1° active TB (HIV, infants)
  - Reactivation
  - Innately immune (presumed) (TST and IGRA: neg)
  - Infection cleared spontaneously
  - Effective adaptive immunity (TST: neg → pos → neg) (IGRA: pos → neg)

- **Primary tuberculous infection**
  - Not infected
  - 1° active TB (HIV, infants)
  - Reactivation
  - Innately immune (presumed) (TST and IGRA: neg)
  - Infection cleared spontaneously
  - Effective adaptive immunity (TST: neg → pos → neg) (IGRA: pos → neg)

- **Latent tuberculous infection**
  - Not infected
  - 1° active TB (HIV, infants)
  - Reactivation
  - Innately immune (presumed) (TST and IGRA: neg)
  - Infection cleared spontaneously
  - Effective adaptive immunity (TST: neg → pos → neg) (IGRA: pos → neg)

Ewer K et al. AJRCCM 2006; 174: 831
# Spectrum of TB infection and disease in exposed individuals

<table>
<thead>
<tr>
<th>Immunological or disease phenotype</th>
<th>Symptoms?</th>
<th>TST</th>
<th>IGRA</th>
<th>CXR changes?</th>
<th>Bacterial burden</th>
<th>Non-replicating MTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innately immune</td>
<td>No</td>
<td>Neg</td>
<td>Neg</td>
<td>No</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>T cell priming but clearance of infection</td>
<td>No</td>
<td>Neg → Pos → Neg</td>
<td>Pos → Neg</td>
<td>No (± calcified granulomas)</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>T cell priming but LTBI</td>
<td>No</td>
<td>Pos (or Neg)</td>
<td>Pos (or Neg)</td>
<td>No (± calcified granulomas)</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>Active TB disease</td>
<td>Yes</td>
<td>Pos (or Neg)</td>
<td>Pos (or Neg)</td>
<td>Yes</td>
<td>++++</td>
<td>N/A</td>
</tr>
<tr>
<td>Treated TB with resolution</td>
<td>No</td>
<td>Pos (or Neg)</td>
<td>Pos (or Neg)</td>
<td>Yes (may be subtle)</td>
<td>+/-</td>
<td>Possible</td>
</tr>
<tr>
<td>Old untreated TB</td>
<td>No</td>
<td>Pos (or Neg)</td>
<td>Pos (or Neg)</td>
<td>Yes</td>
<td>+/-</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Dheda K et al. Respirology 2010
Overview of the initial innate and adaptive immune responses to *MTB* infection

A central component in the defense against *MTB*

**Diagram:***
- **Antigen-presenting cell** (innate immunity)
- **MHC Class II**
- **TCR**
- **CD4**
- **IFNγ**
- **IL-12**

**T cell** (adaptive immunity)
In contrast to IFN\(\gamma\), the type 1 interferons (IFN\(\alpha\), IFN\(\beta\)) appear to increase susceptibility to TB.

IFN\(\alpha\) and IFN\(\beta\) decrease expression of MHC class II. Thus, IFN\(\alpha\) and IFN\(\beta\) makes macrophages hospitable to *MTB*.

Antonelli LRV et al. Intranasal Poly-IC treatment exacerbates tuberculosis in mice through the pulmonary recruitment of a pathogen-permissive monocyte/macrophage population. *J Clin Invest* 2010; 120: 1674-1682
Innate-adaptive immune interactions are a bit more complicated

Stimulate defensin production and neutrophil recruitment

Peptide antigen

Lipid or glycolipid antigen

Stenger S et al. 1998
Roura-Mir C et al. 2005
Dheda K et al. 2010
Chronology of the TB pathogenesis

Stage 1: Ingestion by resident alveolar macrophages

- MTB killed
- Phagosome-lysosome fusion
- Increased phagosome-lysosome fusion
- Increased antigen-presentation to T cells
- Naïve DC

- MTB killed
- Apoptotic death of macrophages
- Naïve macrophages
- Increased antigen-presentation to T cells

- MTB survives, are released extracellularly, and are taken up by other macrophages
- Necrotic death of macrophages
- Multiplication of MTB

Naïve DC
Stage 2: “Symbiotic” stage - *MTB* multiplies and macrophages accumulate

Blood monocytes migrate into the lungs \( \rightarrow \) differentiate into macrophages

Continued ingestion but no destruction of *MTB*

*MTB* multiplies within inactivated macrophages

Formation of early primary tubercle
Stage 3: Migration of T-cells to the site of infection

T-cells begin to activate macrophages to kill or prevent spread of *MTB*

Granulomas form*

(*MTB* is unable to multiply within the solid caseous material)

Infection is contained

* In AIDS patients, CD4+ lymphopenia results in granuloma breakdown, resulting in the inability to control the primary infection or in reactivation of latent infection.
Stage 4a: Chronic latent TB infection

Solid caseous center remains intact

Any bug that escapes the caseous edge are ingested by highly activated macrophages

Giant cells form (a syncytium of epithelioid macrophages)

If the caseation remains solid and does not liquify, a chronic latent infection is established
Stage 4b: Decline in immunity

Immunosuppression
AIDS, cancer, anti-TNFα, age, malnutrition

Loss of integrity of granuloma

Liquifaction of the caseous material ("caseous necrosis") provides a favorable medium for tremendous multiplication of *M. tb*.

Cavity formation

Rupture and spread to other parts of the lungs and to other individuals
How do antigen-presenting cells recognize *MTB*?

- Fibronectin
- Antigen 85
- Lipoarabinomannan
- Lipoproteins
- Mycobacterial DNA
- Polyionic ligands
- Mannose R
- Scavenger R
- TLR
- NOD2
- Muranyl dipeptide
- SP-A R
- SP-A
- C3b, C2
- CR
- FcγR
- Mannose-binding lectin
Autophagy is another mechanism by which intracellular *MTB* is killed.
Cholesterol - is necessary for health

- Precursor of many gonadal and adrenal hormones.
- Precursor of bile salts ("detergent").
- Precursor of Vitamin D.
- Constitutes ~25% of membrane lipids. It provides rigidity to cell membranes.

Plasma membrane
What is the role of cholesterol in TB?

Cholesterol is required for phagocytosis of MTB!

Cholesterol is required for phagocytosis of MTB!
How would a cholesterol-rich diet affect patients with pulmonary TB?
A Cholesterol-Rich Diet Accelerates Bacteriologic Sterilization in Pulmonary Tuberculosis

Carlos Pérez-Guzmán, MD, MS; Mario H. Vargas, MD, MS, FCCP; Francisco Quiñones, MD, MS; Norma Bazavilcaza, CCN; Adriana Aguilar, RD; and the Instituto Nacional de Enfermedades Respiratorias, Tuberculosis Outpatient Service Team†

- 21 patients with active drug-susceptible TB were hospitalized for 8 weeks during the study period.

- Randomized to either a cholesterol-rich diet (800 mg/day) vs. normal diet (250 mg/day).

- Those who received a cholesterol-rich diet had:
  - Faster conversion of sputum culture to negative.
  - Fewer number of bacilli cultured from sputum at 2 weeks
  - Subjectively, less sputum production
Host molecules shown to be protective against TB

Mouse (mostly knockout studies)

IFNγ
TNFα
IL-12
IL-18 (IFNγ-inducing factor)
IL-1β/IL-1α
Nitric oxide
MHC class II
β2-microglobulin
GM-CSF
CD1d-restricted NKT cells
CD4 (helper T cell)
CD8 (cytotoxic T cell)
CD8 (microbicidal T cell*)
Leptin
? vitamin D

*via production of granulysin and perforin
(both disrupts the membrane of M. tb)

Human

IFNγ
TNFα
CD4
? IL-12**
? vitamin D
? IL-32

**patients with defective IL-12R are more susceptible to mycobacteria
**IL-12 has been used as adjuvant to BCG vaccine with some success
3 molecules that can activate macrophages

- IFN\(\gamma\)
- TNF\(\alpha\)
- Vitamin D
How is IFN$_{\gamma}$ protective against TB?

- IFN$_{\gamma}$
  - Induces IL-32 production
  - Induces TNF$_{\alpha}$ production
  - Inhibits T$_{H2}$ and T$_{reg}$ activation
  - Macrophage activation
    - Production of RNI
    - Increased phagosome-lysosome autophagolysosome fusion
    - Granuloma formation
What is the role of IFN\(_{\gamma}\) in murine TB?

- IFN\(_{\gamma}\) knockout mice are highly susceptible to \(MTB\).
- CD4 or CD8 knockout mice are highly susceptible to \(MTB\).
- IL-18 knockout mice are highly susceptible to \(MTB\).
- IL-12 knockout mice are highly susceptible to \(MTB\).
What is the role of IFN$_\gamma$ in human TB?

**IL-12 deficiency**
An infant girl with IL-12 gene defect developed *disseminated M. bovis* after BCG immunization. She had dramatic improvement to IFN$_\gamma$ therapy.

**STAT1$\alpha$ deficiency**

**Defect in IFN$_\gamma$ secretion**

**IL-12 receptor deficiency**
Abdominal TB
Pulmonary TB in 2 of 3 siblings
IFN\(\gamma\) shows promise in the treatment of TB
(essentially all anecdotal case series)

- **Open-labeled (adjuvant) inhaled IFN\(\gamma\)** (30 x 10^6 IU/wk x 4 wks) “showed efficacy” in 5 patients with MDR-TB (Bellevue, NYC).

- **Open-labeled (adjuvant) intramuscular IFN\(\gamma\)** (7 x 10^6 IU/wk x 1 month, then 3 x 10^6 IU/wk x 6 months) also “showed efficacy” in 8 patients with drug-resistant TB (Havana, Cuba).

- **Aerosolized IFN\(\gamma\)** (2 x 10^6 IU TIW x 6 months) to six patients with recalcitrant MDR-TB (Seoul, Korea). Sputum smears remained persistently positive although radiography improved in 5 patients.

- **Subcutaneous IFN\(\gamma\)** (2 x 10^6 IU TIW x 24 wks) to eight patients with persistently culture +ve MDR-TB (Seoul, Korea). No improvement in clinical, radiologic, microbiologic, or immunologic parameters.

- **Aerosolized IFN\(\gamma\)** (10 x 10^6 IU/wk x 8 wks) + anti-TB drugs to four MDR-TB patients. All improved clinically and microbiologically. One patient had increased numbers of NK cells and CD4+/CD25+ T cells during treatment (Jena, Germany and Loyola University, Illinois).

- **DOTs ± aerosolized or SQ IFN\(\gamma\)1b** (4 x 10^6 IU TIW x 4 months) in 89 patients with cavitary TB. Less inflammatory cytokines in the BAL, increase CD4+ lymphocyte responses to PPD, decrease constitutional symptoms, and faster clearance of MTB with nebulized IFN\(\gamma\) (NYU and South Africa).

Condos R et al. Lancet 1997; 349: 1513
Suarez-Mendez R et al. BMC Infectious Dis 2004; 4:44
Grahmann PR and Braun RK. Int J Tuberc Lung Dis 2008; 12: 636
Dawson R et al. PlosOne 2009; 4: e6984
TNFα and TB

• **Responsible for many clinical manifestations of TB**: fever, night sweats, weight loss, and tissue necrosis.

• **Responsible for host-defense functions against TB**
  
  – **TNFα is critical for granuloma formation and TB control** by increasing the expression of adhesion molecules, NO, chemokines, and chemokine receptors.
  
  – **TNFα helps mediate macrophage apoptosis**, an important feature of granulomas.

• **Mice with genetic disruption for TNFα receptor** have increased morbidity and mortality from TB.

• **Is there a more compelling evidence that TNFα is important in controlling TB in man ...?**
• **Infliximab**: a monoclonal antibody that neutralizes TNFα.

• **Method**: all reported cases of TB following infliximab therapy were examined: 70 patients.

• **Strong circumstantial evidence** that inhibition of TNFα increases the risk of reactivation TB:
  • TB was diagnosed a median of 3 months *after* beginning infliximab.
  • In 48 patients, TB developed after 3 or fewer infusions.
  • 56% had extra-pulmonary TB (vs ~18% for non-HIV individuals)
  • 24% had disseminated disease (vs < 2% for non-HIV individuals).
  • Rate of infliximab-associated TB is ~4X background rate for RA.
How do anti-TNFα agents increase susceptibility to TB?

- Disrupts granuloma as TNFα is required for granuloma integrity.

- Inhibition of apoptosis, a known killing mechanism of MTB as well as a process required for granuloma integrity.

- Reduction in the number of CD8⁺CD45RA⁺ effector memory T cells (Bruns H et al. J Clin Invest 2009).
Heliotherapy was considered an important remedy for TB...is there a rational basis for it?
Vitamin D

Skin
7-dehydro-cholesterol → Cholecalciferol → Liver

Liver

Cholecalciferol

25-(OH) vit D

Cholecalciferol

Kidney

1,25-(OH)2 vit D (calcitriol)

Calcitriol = 1,25-(OH)2 vit D2 or D3

Cholecalciferol = D3
Calciferol = D2

Increases Ca+2 and HPO4-2 absorption from the intestine

Cod liver oil

Cholecalciferol

Property of Presenter
Not for Reproduction
Vitamin D and TB

• 1,25-(OH)₂ D₃ suppresses growth of *M. tb* in macrophages.

• In a study of TB in Gujarati Hindus (strict vegans) in foggy London, vitamin D deficiency was a risk factor for TB.

• In general, dark-skin individuals have lower vitamin D levels and this may account for increased susceptibility for TB.

• A vitamin D receptor polymorphism (*tt* genotype) was protective against TB. In contrast, three other vitamin D receptor polymorphism increased susceptibility to TB.
19 kDa lipoprotein, an *MTB* cell wall component

**Mouse macrophages**

Killing of *MTB* in an **nitric oxide-dependent** fashion

**Human macrophages**

Killing of *MTB* in an **nitric oxide-independent** fashion

A **vitamin D-dependent** killing mechanism…

*Science* 2001; 291: 1544
Vitamin D

Skin
7-dehydrocholesterol → Cholecalciferol → Liver
25-(OH) vit D

Liver
1,25-(OH)₂ vit D (calcitriol)

Kidney
Increase Ca⁺² absorption
Induces production of an antimicrobial peptide (Cathelicidin)

Cod liver oil
Cholecalciferol

TB granuloma
25(OH)D-1α-hydroxylase (induced by IFNγ and TNFα)

Cholecalciferol
Activation of TLR2 by *MTB* induces the Vit D receptor and 25(OH)D-1\(\alpha\)-hydroxylase

Liu PT et al.  
*Science* 2006; 311: 1770
Recent investigations of Vitamin D and TB

- Vitamin D can induce cathelicidin, an antimicrobial peptide that can kill *MTB* (Liu PT et al. *Science* 2006).

- In healthy patients given one large dose of vitamin D (2.5 mg = 100,000 IU), their blood (cells) had greater capacity to inhibit proliferation of *M. bovis*-BCG (Martineau AR et al. *AJRCCM* 2007).

- In a R-DB-PC trial of patients with active TB starting treatment randomized to 100,000 IU of cholecalciferol at start of treatment and at 5 and 8 months, there was *no difference in clinical outcome or mortality* (Wejse C et al. *AJRCCM* 2009).
  - Dose may have been too small and they were treating drug-susceptible TB.

- In a R-DB-PC trial of 126 patients with active *pTB* randomized to 100,000 IU of 25-OH-D$_3$ at Day 0, 14, 28, and 42 of beginning treatment, the median time to sputum culture conversion was 36 days (D$_3$) vs. 44 days (placebo) (p=0.14) (Martineau AR et al. *Lancet* 2011).
  - Only patients with the *tt* genotype for the vit D$_3$ receptor had a significantly shorter time to culture conversion.
  - One confounder is that *MTB* isolates from 4 patients (6%) in the placebo arm were resistant to rifampin whereas none were rifampin resistant in the D$_3$ arm.

- Vit D also accelerated resolution of inflammation as measured by cytokine levels (Coussens AK et al. *PNAS* 2012).
Definition and prevalence of vitamin D deficiency (based on serum level of 25-hydroxyvitamin D)

- **Vit D deficiency**: < 20 ng/mL
- **Vit D insufficiency**: 21-29 ng/mL
- “Normal” laboratory range: 20-100 ng/mL
- “Preferred” vit D level: 30-60 ng/mL
- **Toxic levels**: > 150 ng/mL
- 1 billion people worldwide have vit D deficiency or insufficiency.
  - 40-100% of U.S. and European elderly men and women still living in the community are deficient in vit D.
  - ~50% of adolescents are vit D deficient.
  - 1/3 of healthy students, residents, and attending physicians at a Boston hospital had vit D deficiency, despite drinking a glass of mild daily, taking a MVI daily, and eating salmon at least once weekly.

Should patients with TB take vit D supplementation?

- **No specific recommendations for TB.** What follows is general recommendations for maintaining preferred vit D levels - whether there is TB or not.

- **Not unreasonable to measure 25-OH-vit D** because treatment dose for deficiency is more intensive than maintenance dose.

- **Inadequate sun exposure or aging:**
  - **Deficiency:** 50,000 IU D$_3$ weekly for 8 wks, repeat for another 8 wks if level < 30 ng/mL
  - **Maintenance:** 800-1000 IU D$_3$/day (or 3000 IU D$_2$/day) or 50,000 IU D$_2$ every 2-4 wks.

- **Prudent recommendation:** patient with TB should have their 25-OH-vit D levels checked and supplemented if the level is below 30 ng/mL. Taking excessive vit D to achieve supranormal vit D levels should **NOT** be undertaken because high vit D levels are TOXIC.
Could vitamin C be an important adjunctive treatment for TB?

**Fenton reaction:**

\[
\text{VC} + \text{Fe}^{+3} \rightarrow \text{Fe}^{+2} \\
\text{Fe}^{+2} + \text{O}_2 \rightarrow \text{Fe}^{+3} + \text{superoxide} \\
\text{Superoxide} + \text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \\
\text{H}_2\text{O}_2 + \text{Fe}^{+2} \rightarrow \text{hydroxyl radical} + \text{Fe}^{+3} \\
\text{Hydroxyl radical can be toxic to MTB}
\]

Who should be tested for LTBI and if +ve, should be treated?

<table>
<thead>
<tr>
<th>Cutoff value for positivity</th>
<th>Patient groups</th>
</tr>
</thead>
</table>
| ≥ 5 mm induration | • Recent close contact to an active case of TB  
• HIV-positive (5% conversion rate per year)  
• Apical fibronodular disease consistent with old healed TB  
• Organ transplant recipients  
• anti-TNF<sub>α</sub> therapy |
| ≥ 10 mm | • Recent skin test converter (5% conversion rate in the first year, and 5% over the rest of the person’s lifetime if healthy)  
• Foreign-born persons from high prevalent regions for TB  
• Other high risk groups (homeless, IVDA, alcoholics, nursing home residents, hospital employees)  
• Certain predisposing medical conditions (diabetes mellitus, silicosis, immunosuppressive therapy, dialysis patient, hematologic malignancies, or gastrectomy). |
| ≥ 15 mm | • All others, essentially those who are considered low risk; in essence, these individuals should not be tested in the first place. |
Is being thin a risk factor for TB?

68,754 U.S. Navy Recruits (1949-1951)
Palmer CE et al. Am Rev Tuberc 1957

1,717,655 Norwegiens with compulsory miniature X-rays (1963-1975)
Tverdal A. Eur J Respir Dis 1986
Q: Why are thin individuals more susceptible?

Hypothesis: due to a relative deficiency of leptin

Thus, in humans, the more fat, the higher the leptin levels

Leptin

- **Leptin** is a protein produced by fat cells. Leptin travels to the brain to **induce satiety**.

- **Leptin receptors** are also present on other cell types including T-lymphocytes and macrophages.

- Leptin **biases the immune response** toward the $T_{H1}$ (i.e., $\text{IFN}_\gamma$-producing) phenotype.

- **A mouse with mutation of the leptin gene (ob/ob)** results in leptin-deficiency $\supset$ insatiable appetite and marked obesity.

- **Clarification:**
  
  Leptin-deficient mice
  
  Loss of satiety
  
  Fewer fat cells
  
  Lower leptin levels

**ob/ob**
Leptin biases undifferentiated T cells toward the protective, IFNγ-producing $T_H1$ phenotype
Leptin-deficient (ob/ob) mice

- Thymic atrophy
- Reduced splenic weight
- Reduced number of circulating lymphocytes
- Impaired cellular immune function

Avg Wt: 59 gms
Avg Wt: 30 gms
isoflurane

\[ \text{Intranasal } MTB \]

Sacrificed on Day 1 and Weeks 2, 5, & 10

Lungs homogenate

\[ MTB \text{ quantified} \]

\[ \text{Lung } [\text{IFN}_\gamma] \text{ measured} \]

Survival (Kaplan-Meier)
Leptin-deficient *ob/ob* mice are more susceptible to TB

**CFU/gm lung tissue**

**Survival curve**

- 2/14 (14%) WT mice died
- 5/12 (42%) ob/ob mice died

**IFNγ**

- 2 wk: WT *ob/ob*
- 5 wk: WT *ob/ob*
- 10 wk: WT *ob/ob*
Should smokers be added to the list who should be treated if there is evidence for LTBI?

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• anti-TNFα therapy |
| ≥ 10 mm                     | • **Recent skin test converter** (5% conversion rate in the first year, and 5% over the rest of the person’s lifetime if healthy)  
• **Foreign-born persons** from high prevalent regions for TB  
• **Other high risk groups** (homeless, IVDA, alcoholics, nursing home residents, hospital employees)  
• **Certain predisposing medical conditions** (diabetes mellitus, silicosis, immunosuppressive therapy, dialysis patient, hematologic malignancies, gastrectomy, or smoking(?)). |
| ≥ 15 mm                     | • All others, essentially those who are considered low risk; in essence, these individuals should not be tested in the first place. |
## Relative risk of reactivation TB among certain medical conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced HIV infection</td>
<td>9.9, 9.4 → 57*</td>
</tr>
<tr>
<td>Old healed TB</td>
<td>5.2</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>2.4</td>
</tr>
<tr>
<td>Infliximab therapy</td>
<td>2.0 → ≤25 *</td>
</tr>
<tr>
<td>Poorly controlled diabetes mellitus</td>
<td>1.7</td>
</tr>
<tr>
<td>Silicosis</td>
<td>1.7, 1.3, 1.2</td>
</tr>
<tr>
<td>Underweight (≤ 10% below normal)</td>
<td>1.6</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>1.4, 1.3</td>
</tr>
</tbody>
</table>

\*Horsburgh CR et al. *Am J Respir Crit Care Med* 2010  
**Solovic I et al. *Eur Respir J* 2010  
RR (smoking): 2-3  
Horsburgh CR. *N Engl J Med* 2004
Is there experimental evidence that smoking adversely affects TB?

C57BL/6 mice
170-180 cigarettes/day
5 hrs/day
5 days/week
~3 months
TSP ~ 87-104 mg/m³
Four test questions

Which statement is true about leptin?

a. It skews T cells toward the Th₁ (IFN\(_{\gamma}\)-producing) phenotype.
b. It causes increase appetite and weight gain.
c. Its levels are high in thin individuals.

Which statement is false regarding vit D and TB?

a. Deficiency of sunlight can result in vit D deficiency and theoretically increase the risk for TB.

b. Since it is a water soluble vitamin, it is safe to take vit D in “large” doses.
c. Vit D can induce the production of a protein that can directly kill intracellular \textit{MTB}.
d. Vit D enters the cell nucleus and directly turns on certain genes.

Which statement is true about HIV-AIDS and TB?

a. TB in patients with advanced HIV+ is associated with well-formed granulomas.
b. It illustrates the importance of CD4+ T-cells in the defense against TB.
c. It is associated with increased levels of IFN\(_{\gamma}\).

Theoretically, who is at greater risk for TB?

Supperman

Superman
Thank you!

Eddie Moto
Hunchback of Midvale Community College. In charge of dismissal bell.