Multiple Myeloma

Philip Raftopoulos

Group meeting: March 26th, 2024
What is multiple myeloma?

Multiple myeloma is a cancer that affects bone marrow located differentiated B-cells.
What is multiple myeloma?

Many cancers affect B-cell lineages
What is multiple myeloma?

Many cancers affect B-cell lineages

- **Immature B-cell**
- **Mature B-cell**
- **Plasma Cell**

- **Growth factors**
- **Antigen recognition**
What is multiple myeloma?

Many cancers affect B-cell lineages

- **Immature B-cell**
- **Mature B-cell**
- **Plasma Cell**

Growth factors → Antigen recognition

- Leukemia
- Lymphoma
- Myeloma
What is multiple myeloma?

Many cancers affect B-cell lineages

- Immature B-cell
- Mature B-cell
- Plasma Cell

Growth factors
Antigen recognition

Leukemia
Lymphoma
Myeloma
What is multiple myeloma?

Myeloma cells retain their ability to secrete “antibodies”

Clonal: antibodies of a single type
What is multiple myeloma?

Myeloma cells retain their ability to secrete “antibodies”

Clonal: antibodies of a single type

Organ failure

Amyloidosis
Symptoms of multiple myeloma
Symptoms of multiple myeloma

**CRAB acronym**
- **Calcemia**
- **Renal insufficiency**
- **Anemia**
- **Bone marrow lesions**

Symptoms in almost every patient

**Reduced quality of life for myeloma patients**
Myeloma incidence
Myeloma incidence

Hematological malignancies 2023

- **Leukemia**: 32%
- **Myeloma**: 19%
- **Lymphoma**: 49%

**Myeloma**
- 36,000 yearly US cases

**13,000 deaths expected in 2023**
Progress in disease treatment
Multiple myeloma is incurable

Change in multiple myeloma 5 year survival rate

1975–1977: 24%
2012–2018: 60%

Progress in disease treatment
Factors that play roles in better targeting myelomas
Factors that play roles in better targeting myelomas

1. History
Detailed accounts have allowed us to build a strong repertoire of multiple myeloma phenotypes

2. Genetics
Sequencing has revealed a number of genetic drivers of disease that can be targeted

3. Treatment
Advances in therapies have allowed us to better treat multiple myeloma
combination or condition. In a note with which he favoured me at the time, he says—“I have found albumen in a state before, but never in such large quantity. I regard it as the material, which, if the kidney had done its duty, would have been converted into lithate of ammonia.”

ART. IX.—Remarks on the Pathology of Mollities Ossium.

As in the preceding article reference is made to the observations of Mr Solly on Mollities Ossium, it may render the information communicated by Dr Macintyre, Dr Jones, and Mr Dalrymple more complete, if a short account of the facts observed and the inferences deduced by Mr Solly be subjoined.

The observations of Mr Solly are deduced from two examples of the disease, both taking place in females. One took place in a woman aged twenty-nine, who became insane after an attack of rheumatism, in 1839, and who was successively in St Luke’s Hospital, the Marylebone Infirmary, the Islington Infirmary, the Laminac Asylum at Horzon, and finally at Hanwell, where she died, on the 28th October 1842.

The body, examined on the 29th October, at Hanwell, disclosed the following state of the bones.

The height, measured after death, was four feet two inches. The emaciation was great. The head was large in proportion to the size of the body; the chest was very deformed, pinched up, and projecting anteriorly—very narrow from side to side. The ribs appeared widened; the pelvis extremely narrow. The spine was curved forwards, almost at a right angle in the upper dorsal and cervical regions. Both clavicles were broken and bent at an acute angle. The head of one humerus was swollen; the shaft of the left broken and bent; the radius and ulna were slightly swollen; the right radius broken; the lower extremities enlarged at the epiphyses. The thigh-bones on both sides were broken; that on the left side in one place, that on the right in two places; the fractured portions were held together by the periosteum; but no attempt at union,—no trace of callus was observed. The tibia and fibula in both limbs were bent. All the bones of the extremities could be broken with the slightest force; by merely pressing them between the finger and thumb they gave way, and were cracked like a thin-shelled walnut.

A longitudinal and traverse section of the long bones showed that the cancellous structure was nearly absorbed, a mere shell being

1: History
Timeline of multiple myeloma

Timeline of multiple myeloma

Remains of putative patients
- Egypt, Greece, Rome

Samuel Solly
- Account of Sarah Newbury

1844

The case of Sarah Newbury
The case of Sarah Newbury

St. Thomas Hospital, Southwark, London

- The first well documented case of multiple myeloma
- Published in 1844 by Samuel Solly, a prominent London surgeon

The case of Sarah Newbury

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Newbury’s symptoms

- Began experiencing fatigue in 1840
- Fractured both femurs upon being carried
- Fractured clavicles, radius, humerus and ulna

The case of Sarah Newbury

Sarah Newbury, 1844

Newbury’s diagnosis

- Checks in to St. Thomas’ Hospital on April 15, 1844
- Samuel Solly’s diagnosis is mollities ossium or “softness of the bone”
- Newbury prescribed fruits, herbs, and opiates
- Suddenly dies 5 days later on April 20th

The case of Sarah Newbury

Sarah Newbury, 1844

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What was the cause of death?

The case of Sarah Newbury

Autopsy of Newbury’s bones reveals striking discovery

The case of Sarah Newbury

Autopsy of Newbury’s bones reveals striking discovery

Flesh-like structures

Drawings of Newbury’s bones

The case of Sarah Newbury

Autopsy of Newbury’s bones reveals striking discovery

Flesh-like structures

Similar structures in modern patients

Drawings of Newbury’s bones

Autopsy of present-day patient with multiple myeloma

[Multiple myeloma] “commences with a morbid action of the blood vessels… the earthy matter of the bone is absorbed and thrown out by the kidneys”—1851

Myeloma relies on blood vessel outgrowth for progression

The case of Sarah Newbury

Multiple myeloma “commences with a morbid action of the blood vessels... the earthy matter of the bone is absorbed and thrown out by the kidneys” —1851

Samuel Solly

Myeloma relies on blood vessel outgrowth for progression

~1.5 centuries before the angiogenesis is targeted by drugs

Timeline of multiple myeloma

Remains of putative patients
- Egypt, Greece, Rome

Samuel Solly
Account of Sarah Newbury

1844

Henry Bence Jones
Account of Thomas McBean

1845

The case of Thomas McBean

1800s tradesman
Thomas McBean

Dr. Thomas Watson

McBean’s symptoms

- In September, 1844, he felt as if something “snapped” in his chest
- His chest pain recurs severely in spring, 1845
- Dr. Thomas Watson prescribes **steel and quinine**—seems to temporarily treat the symptoms

The case of Thomas McBean

Fall, 1845–Symptoms return

Harley Street
Collection of private practices in London

The case of Thomas McBean

Fall, 1845–Symptoms return

Harley Street
Collection of private practices in London

William MacIntyre

Thomas Watson

Take urine sample from McBean

Can’t pinpoint its unique characteristics

The case of Thomas McBean

“Dear Dr. Jones,

The tube contains urine of very high specific gravity. When boiled, it becomes slightly opaque. On the addition of nitric acid, it effervesces, assumes a reddish hue, and becomes quite clear; but as it cools, assumes the consistence and appearance which you see. Heat reliquifies it. What is it?”

—William MacIntyre to Henry Bence Jones, 1845

The case of Thomas McBean

Patients

Charles Darwin
Michael Faraday

Henry Bence Jones
The father of clinical chemistry

Wanted to apply chemistry to medicine
Had a strong background in protein analytical techniques

Bence Jone’s conclusions

1. McBean’s urine sample did, in fact, contain protein

Bence Jones conducted the 1800s equivalent of a BCA assay

McBean was excreting 60 grams of protein per day

Bence Jone’s conclusions

1. McBean’s urine sample did, in fact, contain protein

   Bence Jones conducted the 1800s equivalent of a BCA assay

   McBean was excreting 60 grams of protein per day

2. Protein excretion is associated with multiple myeloma

   McBean dies in 1846

   Autopsy reveals mollities ossium

   Bence Jones quickly publishes on the connection

Bence Jone’s conclusions

Protein excreted by myeloma patients

What is Bence Jones Protein?

Bence Jones Protein
Term still used today

Timeline of multiple myeloma

Remains of putative patients
Egypt, Greece, Rome

1844
Samuel Solly
Account of Sarah Newbury

1845
Henry Bence Jones
Account of Thomas McBean

1962
Gerald Edelman
Characterization of Bence Jones Protein

Edelman’s research

Structure of antibody

Edelman’s research

Characterization experiments

Gel electrophoresis

Chromatography

Ultra centrifugation

Bence Jones Protein
Excreted in urine

Edelman’s research

Characterization experiments

Bence Jones Protein
Excreted in urine

Gel electrophoresis
Chromatography
Ultra centrifugation

Light Chain

What is the role of the heavy chain?

Edelman’s research

Serum protein electrophoresis (SPEP)

Edelman’s research

Serum protein electrophoresis (SPEP)

Heavy + light chain = M spike!

Edelman’s research

Myeloma cells

Producing monoclonal antibodies

Bloodstream

Heavy + light chain

Kidneys

light chain
Edelman’s research

Myeloma cells → Producing monoclonal antibodies → Bloodstream → Heavy + light chain → Kidneys → light chain → Renal failure
Summary of multiple myeloma history
Summary of multiple myeloma history

Samuel Solly
The Sarah Newbury case

Henry Bence Jones
The Thomas McBean case

Gerald Edelman
Structure of Bence Jones Protein

Flesh-like bone deposits are characteristic of myelomas

Myeloma patients excrete Bence Jones Protein

Bence Jones Protein is antibody light chain
2: Genetics
The genetic path to myeloma is not straightforward


The genetic path to myeloma is not straightforward

Healthy plasma cell

MGUS

Smouldering myeloma

Multiple myeloma

Monoclonal gammopathy of undetermined significance

Low M spike, but no clinical symptoms


Healthy plasma cell

Monoclonal gammopathy of undetermined significance

Low M spike, but no clinical symptoms

Multiple myeloma

>3% of people over 60 may develop mutations in their plasma cells

Why is this number so high?


Plasma cells are particularly prone to mutation
Plasma cells are particularly prone to mutation

Antigen recognition

B-cell → Plasma cell


Plasma cells are particularly prone to mutation

Antigen recognition
B-cell → Plasma cell

Somatic hyper-mutation

Heavy Chain DNA Locus

Replication with $10^6$ fold more frequent mutations

Accumulated mutations in variable region

Plasma cells are particularly prone to mutation

Double stranded DNA breaks


Plasma cells are particularly prone to mutation

Transcription machinery

Activates downstream genes

Immuno-globulin heavy chain enhancer

Double stranded DNA breaks


Plasma cells are particularly prone to mutation


Plasma cells are particularly prone to mutation

Transcription machinery

Activates downstream genes

IGH

Immuno-globulin heavy chain enhancer

Oncogene

Gene translocation from other mutations


Plasma cells are particularly prone to mutation

Transcription machinery

Activates downstream genes

IGH

Immuno-globulin heavy chain enhancer

Oncogene

Gene translocation from other mutations

Up-regulated oncogene, cancerous phenotype


What oncogene translocations generally result in myeloma?
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- **CCND1 (Cyclin D1)**, ~20% of myelomas
- **MMSET** (Multiple Myeloma SET domain protein), ~15% of myelomas
- **MAF (c-MAF)**, ~15% of myelomas

References:


What oncogene translocations generally result in myeloma?

- CCND1 (Cyclin D1) is present in ~20% of myelomas.
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- MAF (c-MAF) is present in ~15% of myelomas.


The role of cyclin D1 in multiple myeloma
The role of cyclin D1 in multiple myeloma

Cyclins play a large role in regulating the cell cycle.

The process that governs cell division

The role of cyclin D1 in multiple myeloma

Additional roles of CCND1
The role of cyclin D1 in multiple myeloma

Additional roles of CCND1

Interfacing with other transcription factors

ER-α  AR

Increased angiogenesis

Attraction of blood vessels and nutrients towards cancer


The role of cyclin D1 in multiple myeloma

Additional roles of CCND1

Interfacing with other transcription factors
- ER-α
- AR

Increased angiogenesis
Attraction of blood vessels and nutrients towards cancer

Sensitizing myeloma cells to stress
- Accumulated misfolded proteins
- Cell death

The role of cyclin D1 in multiple myeloma

Additional roles of CCND1

Interfacing with other transcription factors

ER-α

AR

Increased angiogenesis

Attraction of blood vessels and nutrients towards cancer

Sensitizing myeloma cells to stress

Accumulated misfolded proteins

Cell death

Associated with better outcomes


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The role of MMSET in multiple myeloma

Histone methyltransferase


The role of MMSET in multiple myeloma

Histone methyltransferase

MMSET

H3K36me2
Di-methylation of K36 on H3

Epigenetic remodeling

- **Increased** cyclins, growth factors
- **Decreased** repressive histone markers


The role of MMSET in multiple myeloma

MMSET

Histone methyltransferase

H3K36me2
Di-methylation of K36 on H3

H4K20me3
Tri-methylation of K20 on H4

Epigenetic remodeling
- Increased cyclins, growth factors
- Decreased repressive histone markers

DNA damage resistance
- Decreased apoptosis
- Poor response to treatment regimens

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The role of MAF in multiple myeloma

- c-MAF: Master regulator of mitogenic genes in plasma cells

- Up-regulation of integrins: Cell adhesion proteins


Jiang, Q.; Mao, H.; He, G.; Mao, X. Cancer Letters 2022, 543, 215791.
The role of MAF in multiple myeloma

Master regulator of mitogenic genes in plasma cells

Up-regulation of integrins:
Cell adhesion proteins

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The role of MAF in multiple myeloma

- c-MAF: Master regulator of mitogenic genes in plasma cells
- Up-regulation of integrins: Cell adhesion proteins
- Self adhesion
- Extensive migration
- Resistance to therapies


Jiang, Q.; Mao, H.; He, G.; Mao, X. *Cancer Letters* 2022, 543, 215791.
The role of MAF in multiple myeloma


The role of MAF in multiple myeloma

Targeting c-MAF could both kill myeloma cells and activate the immune system.


Jiang, Q.; Mao, H.; He, G.; Mao, X. Cancer Letters 2022, 543, 215791.
IRF4 is up-regulated in multiple myeloma

IRF4
Interferon regulatory factor 4
Can be up-regulated in a variety of different ways

IRF4 is up-regulated in multiple myeloma

Pro-growth signals


IRF4 is up-regulated in multiple myeloma

3: Treatment
Initial treatment often includes stem cell transplant

**Autologous stem cell transplant**

Bone marrow fully depleted, replaced by one's own stem cells
Types of treatment for multiple myeloma

1. IMiDs
2. Proteasome inhibitors
3. Dexamethasone
4. Novel therapeutics
Types of treatment for multiple myeloma

1. IMiDs
2. Proteasome inhibitors
3. Dexamethasone
4. Novel therapeutics
**Immunomodulatory Imide Drugs: Molecular Glues that Bind Cereblon**

**Thalidomide**

*Morning sickness (1957)*

**1960s**

*Thalidomide induces Birth Defects*
Immunomodulatory Imide Drugs (IMiDs)

Thalidomide
*Cancer treatment (1991)*

1960s
*Thalidomide induces Birth Defects*

Multiple Myeloma
*B cell cancer*

Bristol Myers Squibb

*Immunomodulatory Imide Drugs: Molecular Glues that Bind Cereblon*
Immunomodulatory Imide Drugs: Molecular Glues that Bind Cereblon

Immunomodulatory Imide Drugs (IMiDs)

- **Thalidomide**
  - Cancer treatment (1991)
- **Lenalidomide**
  - $10.1 billion in sales (2022)
- **Pomalidomide**
  - $3.5 billion in sales (2022)

1960s
- **Thalidomide** induces Birth Defects

Multiple Myeloma
- **B cell cancer**

1960s
- Thalidomide induces Birth Defects

Cancer treatment (1991)
- $3.5 billion in sales (2022)

Multiple Myeloma
- B cell cancer
Immunomodulatory Imide Drugs: Molecular Glues that Bind Cereblon

Immunomodulatory Imide Drugs: Molecular Glues that Bind Cereblon

Cereblon is an adaptor for the Cullin Ring E3 Ligase Complex

IMiDs function as Molecular Glues to Induce Targeted Protein Degradation

Mechanism of Action

IKZF1, IKZF3
CRBN
Cereblon E3 ligase complex

IMiDs function as Molecular Glues to Induce Targeted Protein Degradation

**Mechanism of Action**

IKZF1, IKZF3, CRBN

Cereblon E3 ligase complex

Ternary complex formation


**IMiDs function as Molecular Glues to Induce Targeted Protein Degradation**

IKZF1, IKZF3

CRBN

**Mechanism of Action**

Cereblon E3 ligase complex

Ternary complex formation

Poly-ubiquitination

Proteasomal Degradation


What is the consequence of degrading IKZF1 and IKZF3?

What is the consequence of degrading IKZF1 and IKZF3?

Transcriptionally up-regulate

Ikaros / Aiolos

IKZF1 / IKZF3

IRF4

Myeloma driver

Drives T-cell exhaustion

Therapeutic relevance of IRF4 inhibition

Therapeutic relevance of IRF4 inhibition

Therapeutic relevance of IRF4 inhibition

How important is IRF4 for IMiD mediated cell death?

Myeloma Cell Death
- Apoptosis
- Growth Inhibition

Immune cell activation
- T cell and NK cell activation
- IL-2 and IFN-γ secretion

IMiDs function as Molecular Glues to Induce Targeted Protein Degradation

IMiDs function as Molecular Glues to Induce Targeted Protein Degradation


Len-sensitive
IMiDs function as Molecular Glues to Induce Targeted Protein Degradation

IMiDs function as Molecular Glues to Induce Targeted Protein Degradation

“...antiproliferative effects of this drug involves at least one target other than IRF4.”

Additional mechanisms beyond IRF4

CRBN–MCT1–CD147 complex

Lactate transport, myeloma growth

Additional mechanisms beyond IRF4

**CRBN–MCT1–CD147 complex**

Lactate transport, myeloma growth

**Lenalidomide**

Complex destabilization

*Anti-myeloma effects*

Additional mechanisms beyond IRF4

CRBN–HSP90 complex

Co-chaperoning complex
Helps stabilize membrane proteins

Additional mechanisms beyond IRF4

CRBN–HSP90 complex

HSP90

CRBN

Co-chaperoning complex
Helps stabilize membrane proteins

Lenalidomide

Complex destabilization

Additional mechanisms beyond IRF4

**Co-chaperoning complex**
Helps stabilize membrane proteins

**CRBN–HSP90 complex**

**Lenalidomide**

**Complex destabilization**

**Misfolded**
LAT1, CD98, etc.

**Destabilization of chaperone targets**
Anti-myeloma effects

Types of treatment for multiple myeloma

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Types of treatment for multiple myeloma

1. IMiDs

2. Proteasome inhibitors

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4. Novel therapeutics
Proteasome inhibitors

Carfilzomib

Bortezomib
Proteasome inhibitors

How the majority of proteins are degraded

Proteasome inhibitors

How the majority of proteins are degraded

Particularly prone to apoptosis

Proteasome inhibitors

IMiDs rely on the 26S Proteasome for degradation of IKZF1/3

26S Proteasome
How the majority of proteins are degraded
Proteasome inhibitors

IMiDs rely on the 26S Proteasome for degradation of IKZF1/3

IKZF1/3

26S Proteasome
How the majority of proteins are degraded

Proteasomal degradation
**Proteasome inhibitors**

**IMiDs rely on the 26S Proteasome for degradation of IKZF1/3**

IMiDs + proteasome inhibitors should be theoretically incompatible
IMiDs and proteasome inhibitors exhibit synergy in treating multiple myeloma
IMiDs and proteasome inhibitors exhibit synergy in treating multiple myeloma

Lenalidomide

Bortezomib

Increased apoptosis
Compared to monotherapy

IMiDs and proteasome inhibitors exhibit synergy in treating multiple myeloma

IKZF1 degradation is maintained upon co-treatment

IMiDs and proteasome inhibitors exhibit synergy in treating multiple myeloma

IKZF1 degradation is maintained upon co-treatment

Degradation is dependent on calpain proteases

Dexamethasone also exhibits synergy with IMiDs and proteasome inhibitors
Dexamethasone also exhibits synergy with IMiDs and proteasome inhibitors

- **Dexamethasone**: Immunosuppressant
- **Lenalidomide**: Proteasomal degrader, Immuno stimulant
- **Bortezomib**: Proteasome inhibitor
Dexamethasone also exhibits synergy with IMiDs and proteasome inhibitors
Dexamethasone also exhibits synergy with IMiDs and proteasome inhibitors

Synergistic effect still seen despite possible therapeutic conflicts
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CeLMODs: Next generation IMiDs

Stronger binders of CRBN than IMiDs
Cell surface targets have been employed to target multiple myeloma

- **BCMA**: Antibody-drug conjugate, CAR-T, Bispecific antibody
- **CD38**: Monoclonal antibody
- **CD47**: Monoclonal antibody
- **CD138**: Antibody drug conjugate
- **GPR5D**: Monoclonal antibody, CAR-T
Questions