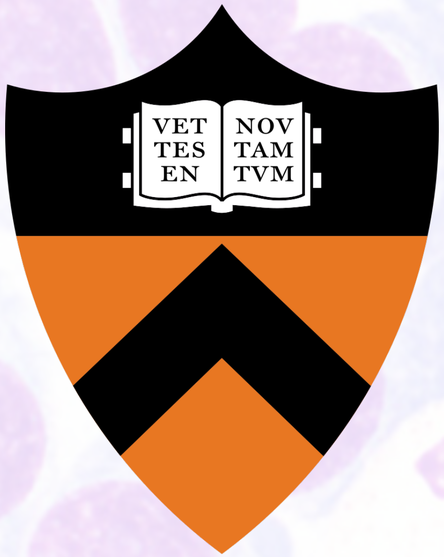
Multiple Myeloma

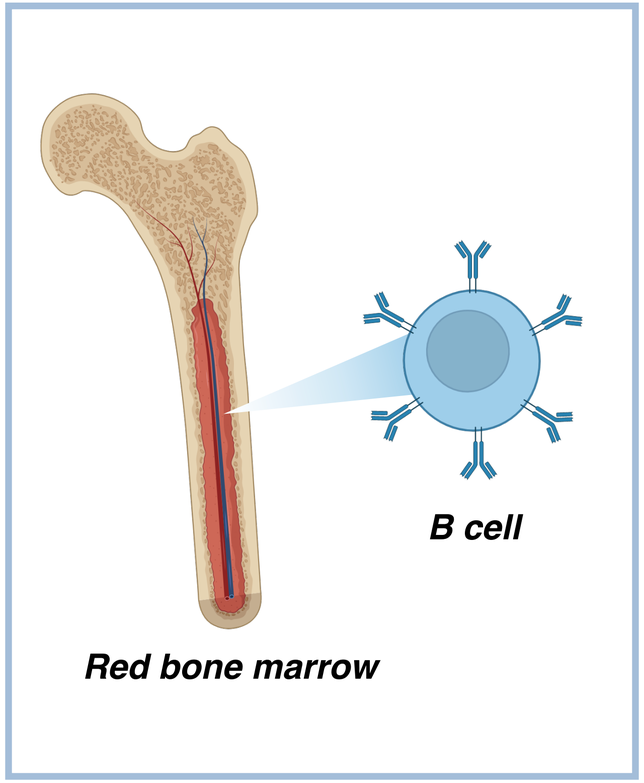


Philip Raftopoulos

Group meeting: March 26th, 2024

What is multiple myeloma?

Hematological malignancies



Multiple myeloma is a cancer that affects
bone-marrow *located* ***differentiated B-cells***

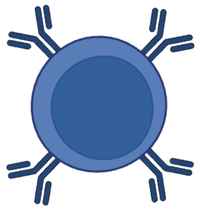
What is multiple myeloma?

Many cancers affect B-cell lineages

What is multiple myeloma?

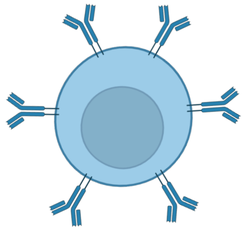
Many cancers affect B-cell lineages

Immature B-cell



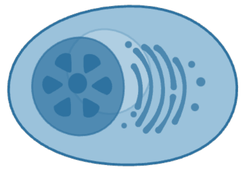
Growth factors

Mature B-cell



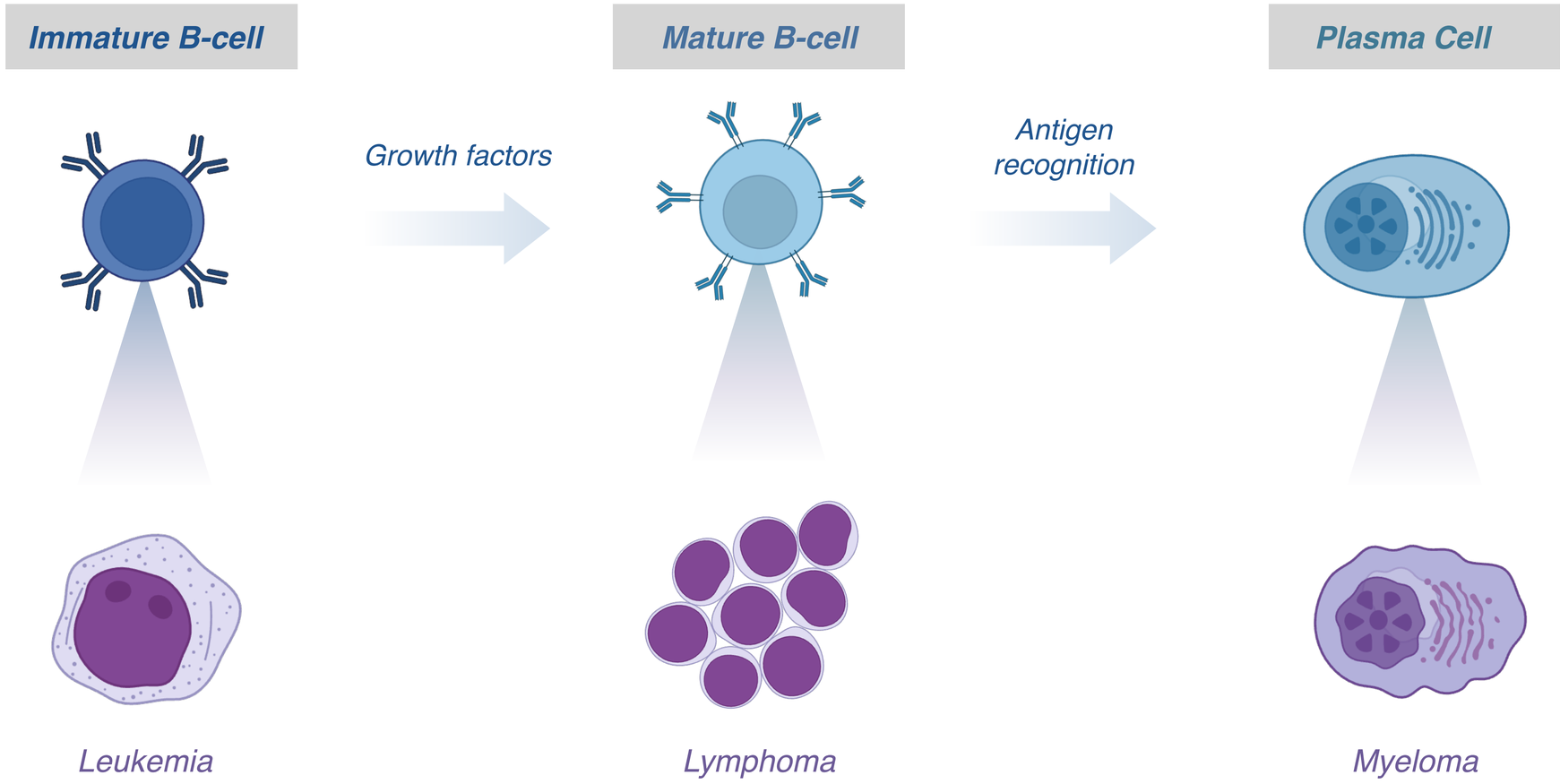
Antigen recognition

Plasma Cell



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

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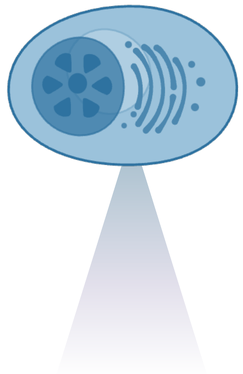
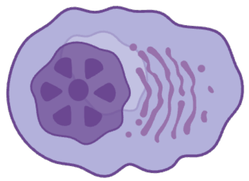


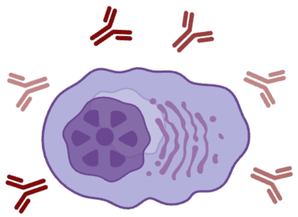


Leukemia

Lymphoma

Myeloma

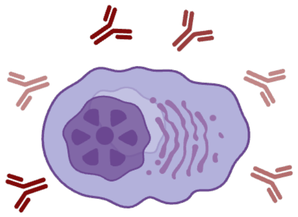
What is multiple myeloma?



Myeloma cells retain their ability to secrete “antibodies”

Clonal: antibodies of a single type

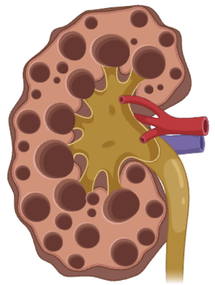
What is multiple myeloma?

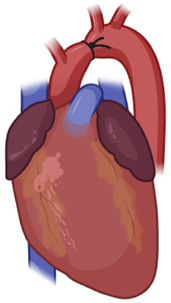


Myeloma cells retain their ability to secrete “antibodies”

Clonal: antibodies of a single type

Organ failure





Amyloidosis

Symptoms of multiple myeloma

Symptoms of multiple myeloma

***CRAB** acronym*

***C**alcemia*

***R**enal insufficiency*

***A**nemia*

***B**one marrow lesions*

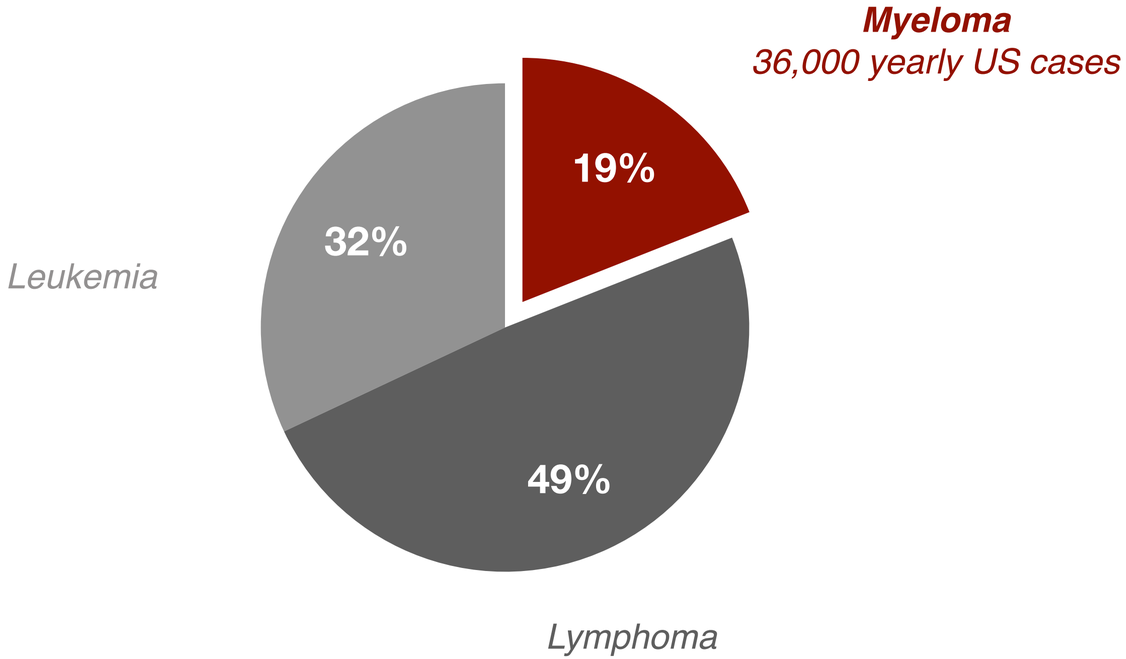
Symptoms in almost every patient

Reduced quality of life for myeloma patients

Myeloma incidence

Myeloma incidence

Hematological malignancies 2023



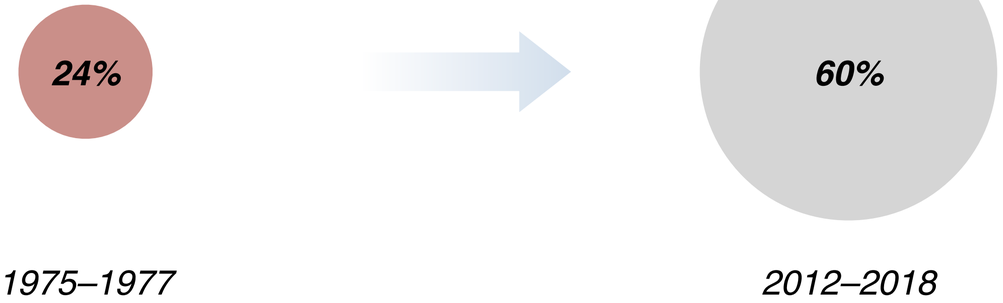
13,000 deaths expected in 2023

Progress in disease treatment

Progress in disease treatment

*Multiple myeloma is **incurable***

Change in multiple myeloma 5 year survival rate



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

1: History

combination or condition. In a note with which he favoured me at the time, he says—"I have found albumen in this 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. By SAMUEL SOLLY, F.R.S., &c. (Medico-Chirurgical Transactions. Vol. xxvii. London 1844.) [Abstract.]

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 Lunatic Asylum at Hoxton, 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 much 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 swelled; the shaft of the left broken and bent; the radius and ulna were slightly swelled; the right radius broken; the lower extremities enlarged at the epiphyses. The thigh-bones on both sides were broken; that on the right side in one place, that on the left 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 transverse section of the long bones showed that the osseous structure was nearly absorbed, a mere shell being

Mr Solly *on Mollities Ossiu*

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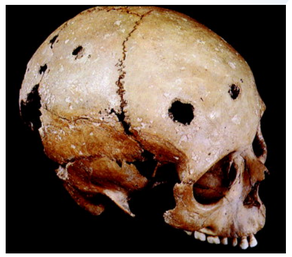
Timeline of multiple myeloma

1844

Ancient Times



Remains of putative patients

Egypt, Greece, Rome

Samuel Solly

Account of Sarah Newbury

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The case of Sarah Newbury

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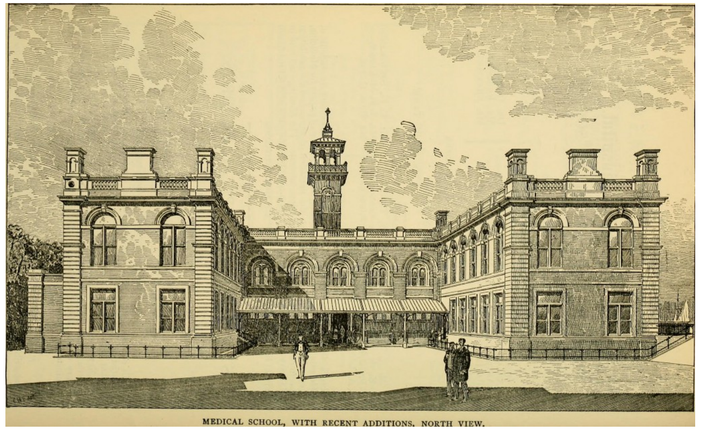
MEDICAL SCHOOL, WITH RECENT ADDITIONS. NORTH VIEW.

St. Thomas Hospital, Southwark, London

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

Kyle, R. A.; Steensma, D. P. “History of Multiple Myeloma.” In *Multiple Myeloma*; Moehler, T., Goldschmidt, H., Eds.; Springer: Berlin, Heidelberg, **2011**; pp 3–23.

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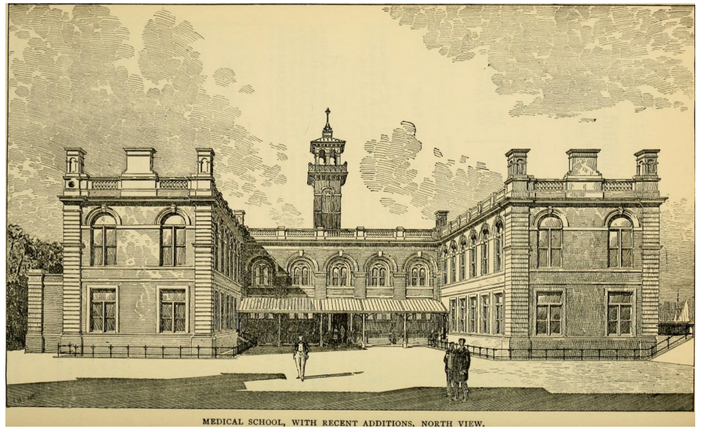

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1800s housewife

Newbury's symptoms

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

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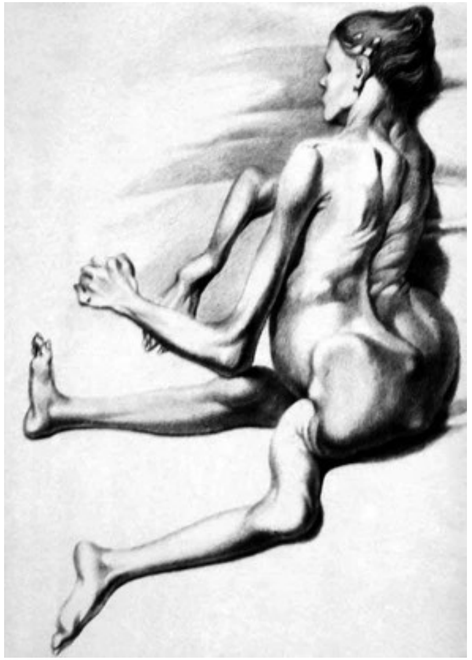

Sarah Newbury, 1844

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

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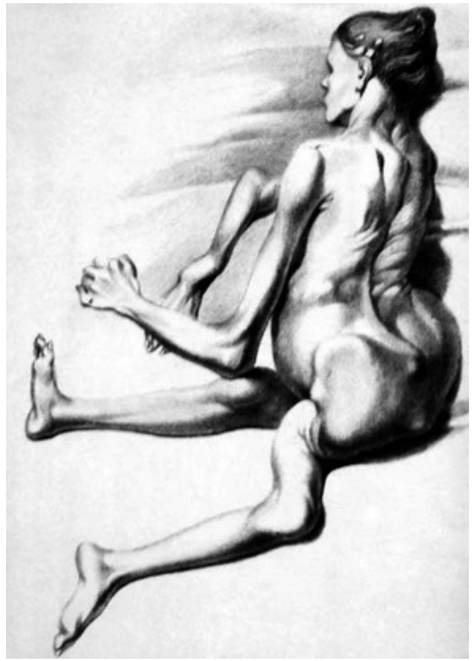

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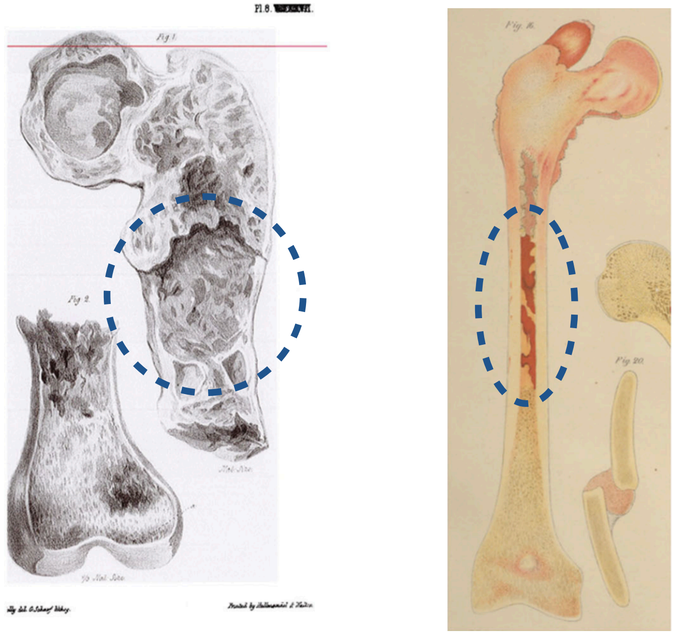
Autopsy of Newbury's bones reveals striking discovery

Mulligan, M.; Bonar, F.; Fanburg-Smith, J.; Melhem, L.; Messiou, C.; Kocoglu, M.; Streeten, E. *Cancer Investigation* **2022**, *40* (6), 544–553.

The case of Sarah Newbury

Autopsy of Newbury's bones reveals striking discovery

Flesh-like structures



Drawings of **Newbury's bones**

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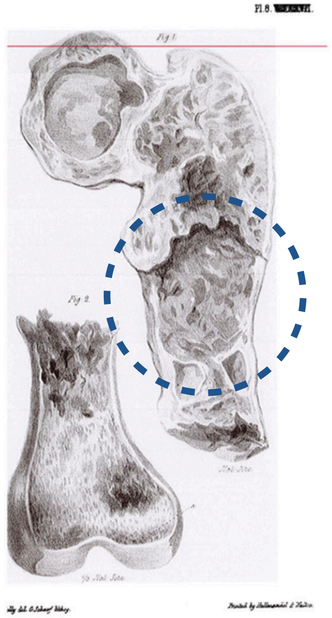

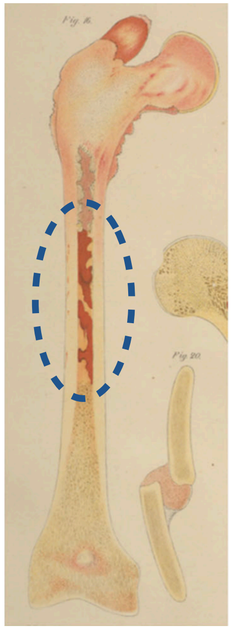

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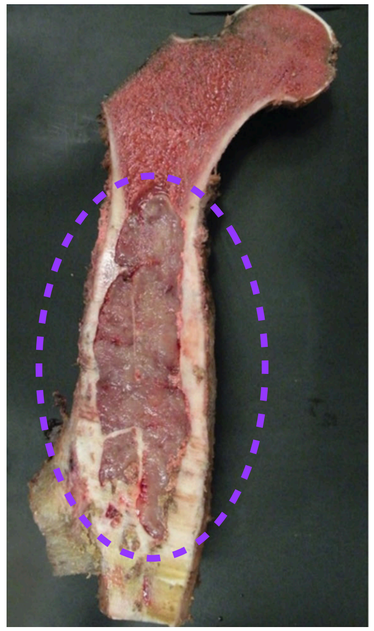

Autopsy of **present-day patient** with multiple myeloma

Similar structures in modern patients

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Samuel Solly

*[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

Solly, S. *Edinb Med Surg J* **1851**, *75* (186), 173–178.

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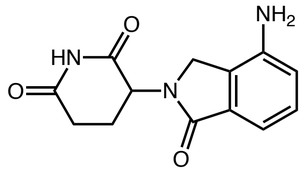


~1.5 centuries before the angiogenesis is targeted by drugs

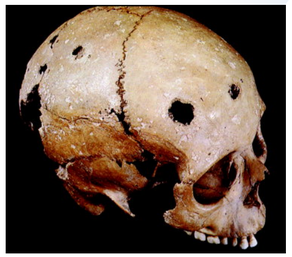
Solly, S. *Edinb Med Surg J* **1851**, *75* (186), 173–178.

Timeline of multiple myeloma

Ancient Times

1844

1845



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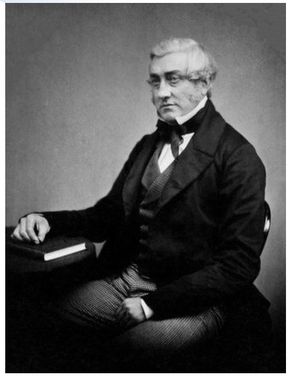

Henry Bence Jones

Account of Thomas McBean

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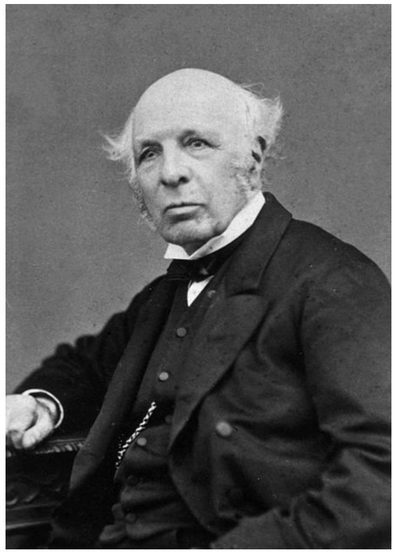
The case of Thomas McBean

1800s tradesman
Thomas McBean

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



Dr. Thomas Watson

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The case of Thomas McBean

Fall, 1845–Symptoms return

Harley Street

Collection of private practices in London

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The case of Thomas McBean

Fall, 1845–Symptoms return

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William MacIntyre

Thomas Watson

Take urine sample from McBean

Can’t pinpoint its unique characteristics

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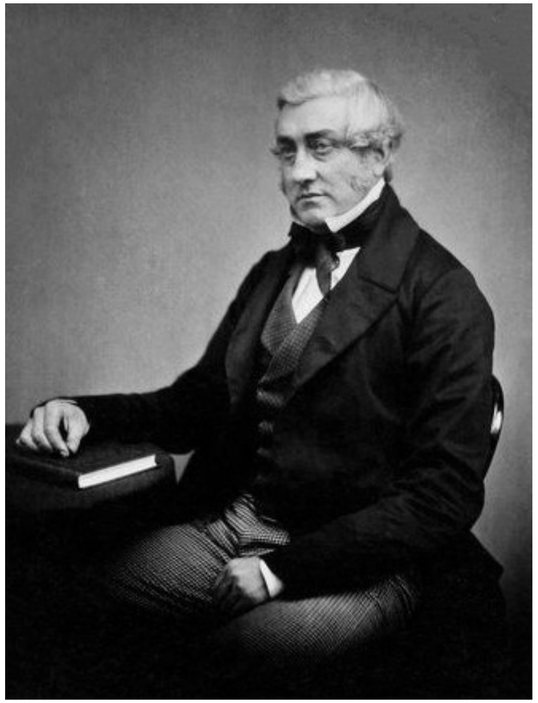

Henry Bence Jones

“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**

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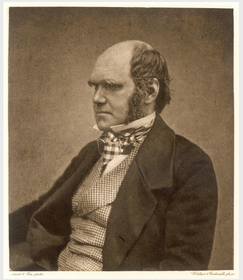
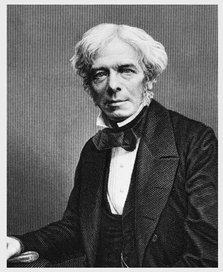
The case of Thomas McBean

Patients



Charles Darwin



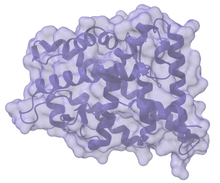
Michael Faraday

Henry Bence Jones

The father of clinical chemistry

*Wanted to apply **chemistry** to **medicine***

*Had a strong background in **protein** analytical techniques*



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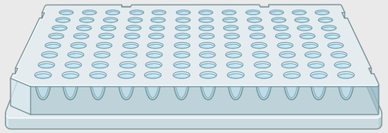
Bence Jone's conclusions

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*

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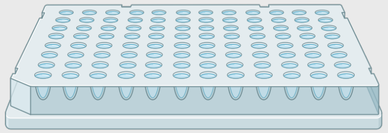
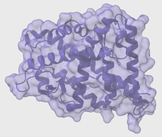


*Bence Jones conducted the 1800s equivalent of a **BCA assay***



*McBean was excreting **60 grams** of protein per day*

2 *Protein excretion is associated with multiple myeloma*

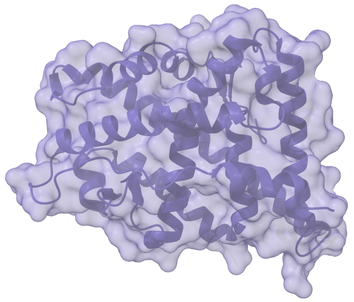
*McBean dies in **1846***

*Autopsy reveals **mollities ossium***

Bence Jones quickly publishes on the connection

Kyle, R. A.; Steensma, D. P. "History of Multiple Myeloma." In *Multiple Myeloma*; Moehler, T., Goldschmidt, H., Eds.; Springer: Berlin, Heidelberg, **2011**; pp 3–23.

Bence Jone's conclusions



Protein excreted by myeloma patients

Bence Jones Protein

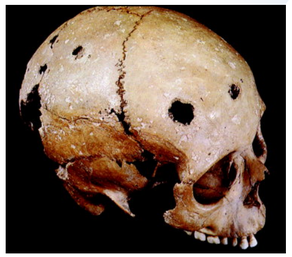
Term still used today

What is Bence Jones Protein?

Kyle, R. A.; Steensma, D. P. "History of Multiple Myeloma." In *Multiple Myeloma*; Moehler, T., Goldschmidt, H., Eds.; Springer: Berlin, Heidelberg, **2011**; pp 3–23.

Timeline of multiple myeloma

Ancient Times



Remains of putative patients

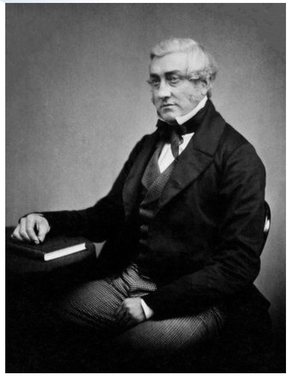
Egypt, Greece, Rome

1844

1845

Samuel Solly

Account of Sarah Newbury



Henry Bence Jones

Account of Thomas McBean

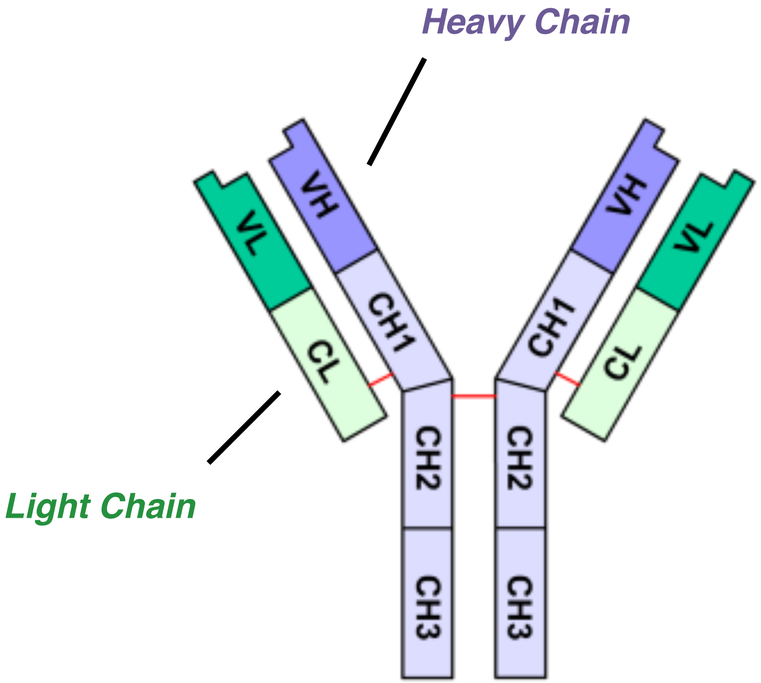
1962

Gerald Edelman

Characterization of Bence Jones Protein

Kyle, R. A.; Steensma, D. P. “History of Multiple Myeloma.” In *Multiple Myeloma*; Moehler, T., Goldschmidt, H., Eds.; Springer: Berlin, Heidelberg, **2011**; pp 3–23.

Edelman's research



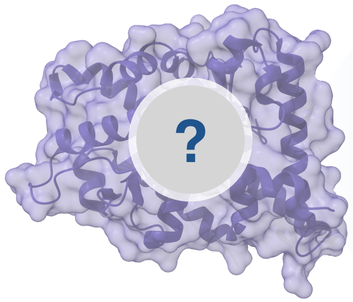
Structure of antibody

Nobel Prize
Physiology / Medicine
1972

Edelman, G. M.; Benacerraf, B.; Ovary, Z.; Poulik M. D. *Proc Natl Acad Sci U S A* **1961**, *47*, 1751–1758.

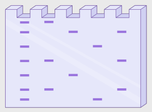
Edelman's research

Characterization experiments

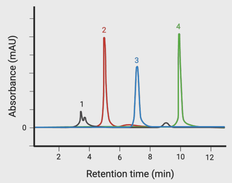


Bence Jones Protein

Excreted in urine



Gel electrophoresis



Chromatography

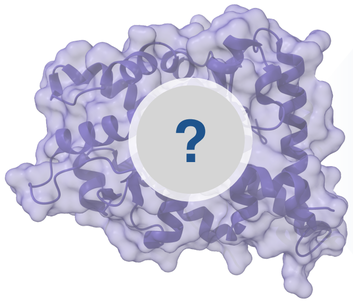
Ultra centrifugation

Light Chain

Ramakrishnan, N.; Jialal, I. "Bence-Jones Protein." In *StatPearls*; StatPearls Publishing: Treasure Island (FL), **2024**.

Edelman's research

Characterization experiments



Bence Jones Protein

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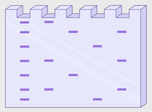

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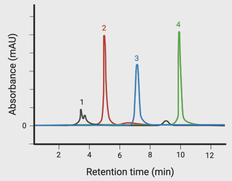

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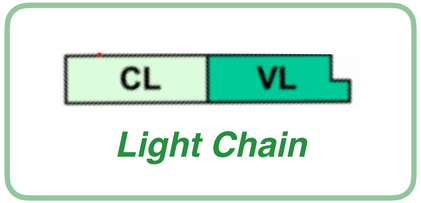
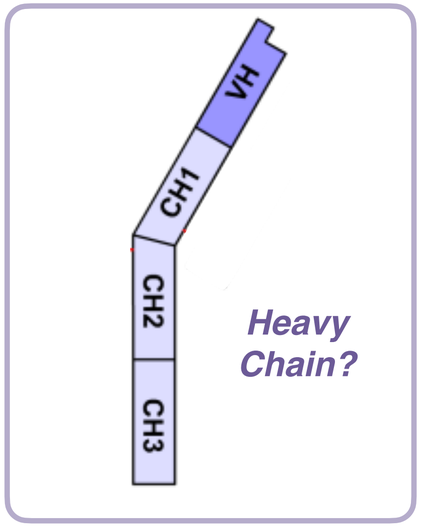
Ultra centrifugation



Light Chain



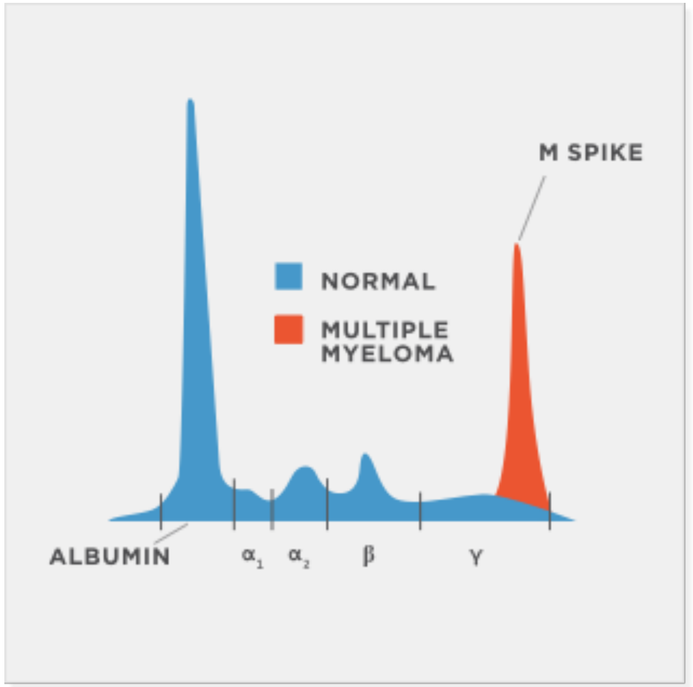
Heavy Chain?

What is the role of the heavy chain?

Ramakrishnan, N.; Jialal, I. "Bence-Jones Protein." In *StatPearls*; StatPearls Publishing: Treasure Island (FL), **2024**.

Edelman's research

Serum protein electrophoresis (SPEP)



Ramakrishnan, N.; Jialal, I. "Bence-Jones Protein." In *StatPearls*; StatPearls Publishing: Treasure Island (FL), **2024**.

Edelman's research

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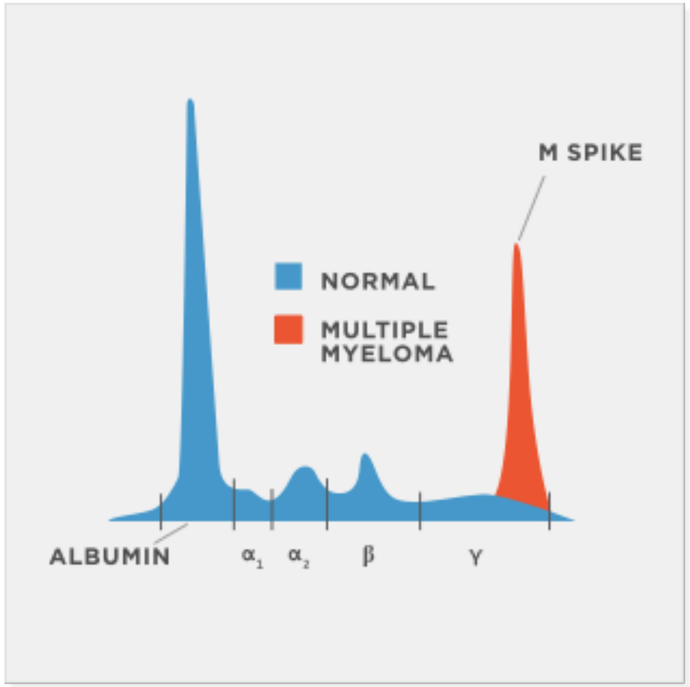
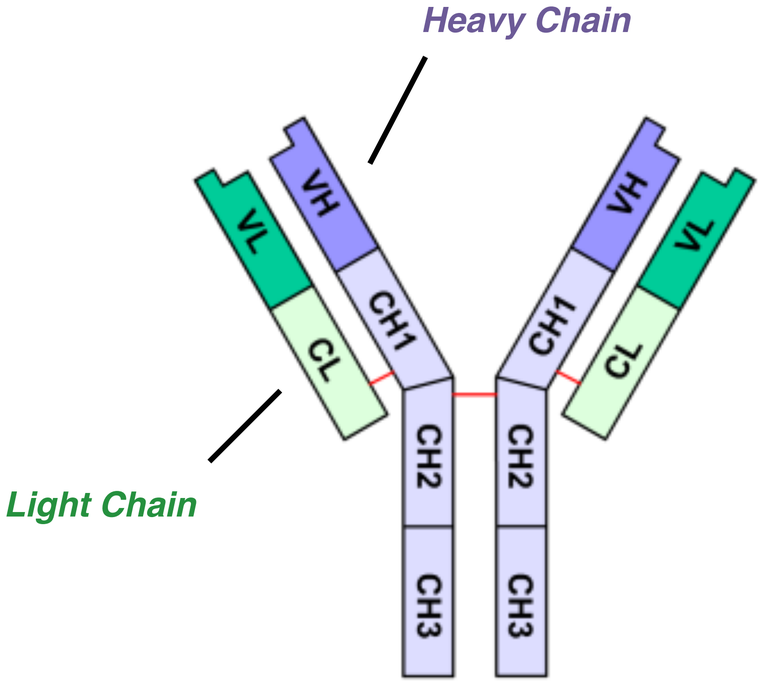


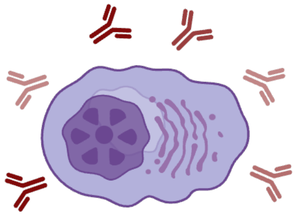


Heavy + light chain = M spike!

Ramakrishnan, N.; Jialal, I. "Bence-Jones Protein." In *StatPearls*; StatPearls Publishing: Treasure Island (FL), **2024**.

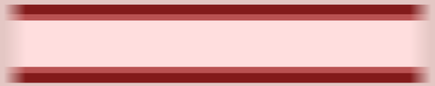
Edelman's research

Myeloma cells



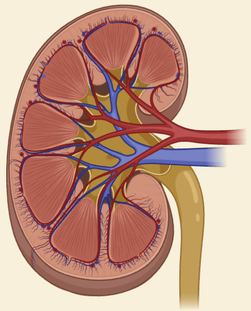
Producing monoclonal antibodies

Bloodstream



Heavy + light chain

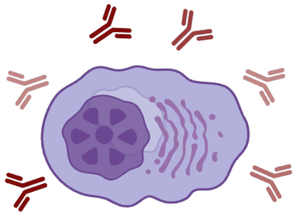
Kidneys



light chain

Edelman's research

Myeloma cells



Producing monoclonal antibodies

Bloodstream

Heavy + light chain

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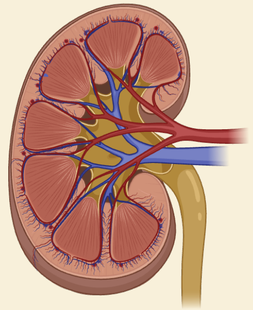
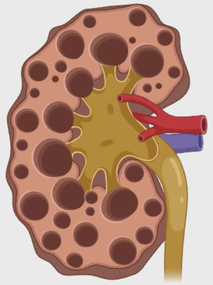


light chain

Renal failure

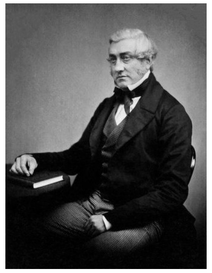


Summary of multiple myeloma history

Summary of multiple myeloma history

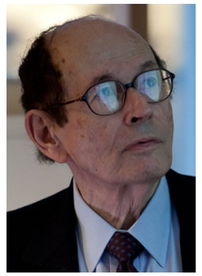
Samuel Solly
The Sarah Newbury case

Flesh-like bone deposits are characteristic of myelomas



Henry Bence Jones
The Thomas McBean case

Myeloma patients excrete Bence Jones Protein



Gerald Edelman
Structure of Bence Jones Protein

Bence Jones Protein is antibody light chain

2: Genetics

The genetic path to myeloma is not straightforward

Kumar, S. K.; Rajkumar, V.; et. al. *Nat Rev Dis Primers* **2017**, *3* (1), 1–20.

Morgan, G. J.; Walker, B. A.; Davies, F. E. *Nat Rev Cancer* **2012**, *12* (5), 335–348.

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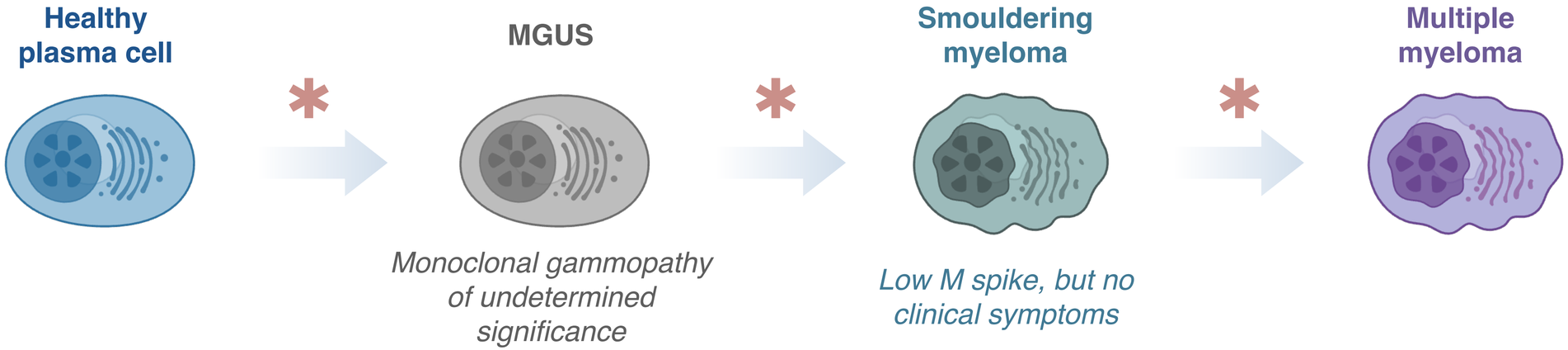

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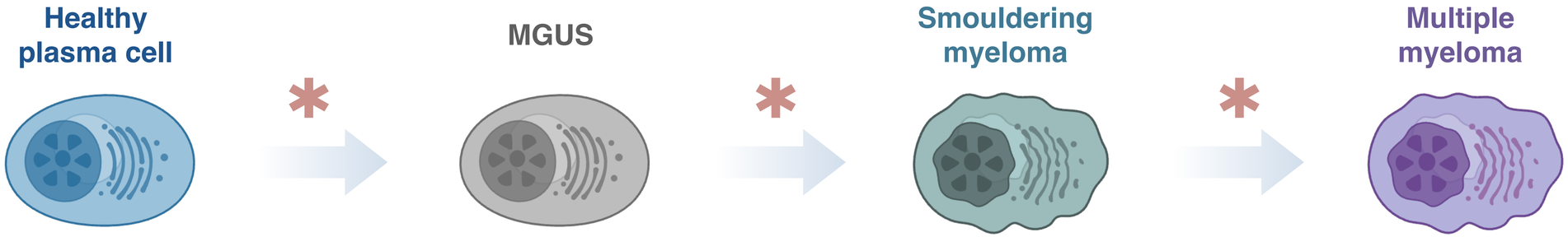

>3% of people over 60 may develop mutations in their plasma cells

Why is this number so high?

Kumar, S. K.; Rajkumar, V.; et. al. *Nat Rev Dis Primers* **2017**, *3* (1), 1–20.

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Plasma cells are particularly prone to mutation

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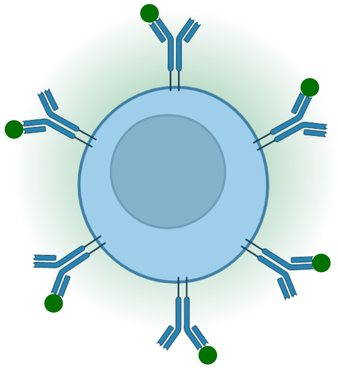

Antigen recognition

B-cell ⟶ Plasma cell

Kumar, S. K.; Rajkumar, V.; et. al. *Nat Rev Dis Primers* **2017**, *3* (1), 1–20.

Morgan, G. J.; Walker, B. A.; Davies, F. E. *Nat Rev Cancer* **2012**, *12* (5), 335–348.

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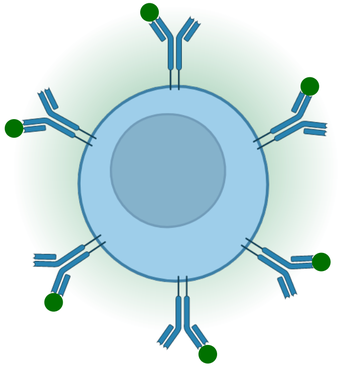
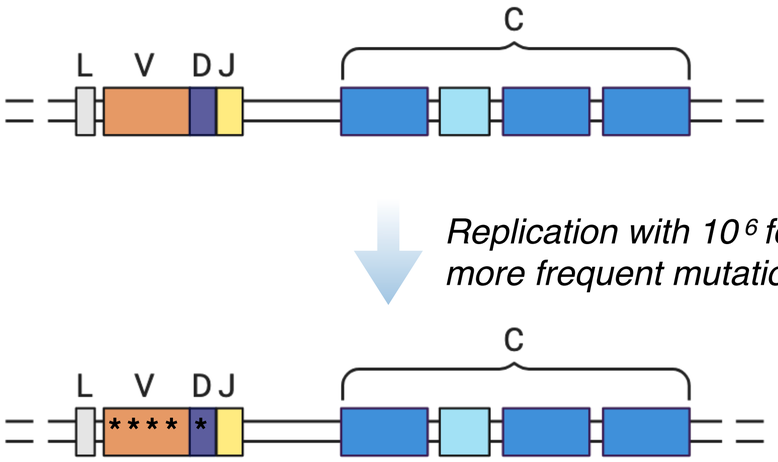


Antigen recognition

B-cell ⟶ Plasma cell

Somatic hyper-mutation

Heavy Chain DNA Locus



Accumulated mutations in variable region

Kumar, S. K.; Rajkumar, V.; et. al. *Nat Rev Dis Primers* **2017**, *3* (1), 1–20.

Morgan, G. J.; Walker, B. A.; Davies, F. E. *Nat Rev Cancer* **2012**, *12* (5), 335–348.

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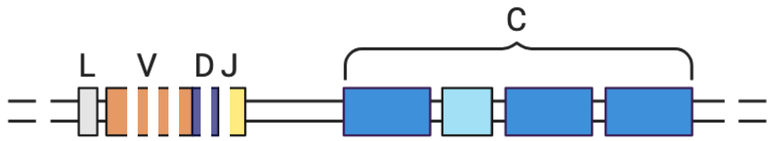
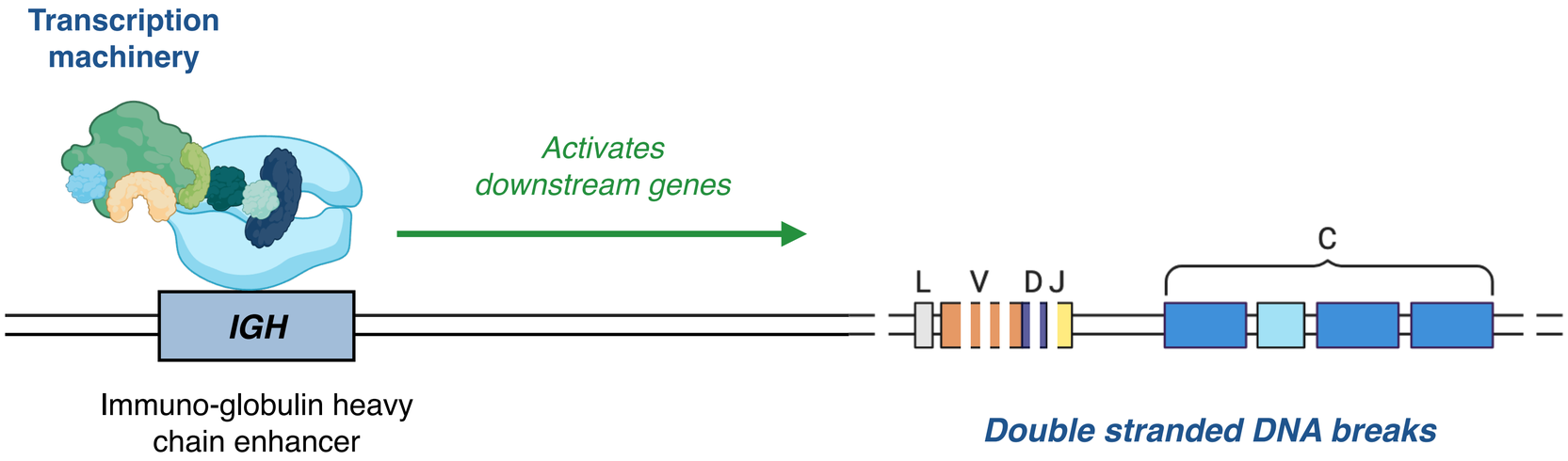


Double stranded DNA breaks

Kumar, S. K.; Rajkumar, V.; et. al. *Nat Rev Dis Primers* **2017**, *3* (1), 1–20.

Morgan, G. J.; Walker, B. A.; Davies, F. E. *Nat Rev Cancer* **2012**, *12* (5), 335–348.

Plasma cells are particularly prone to mutation



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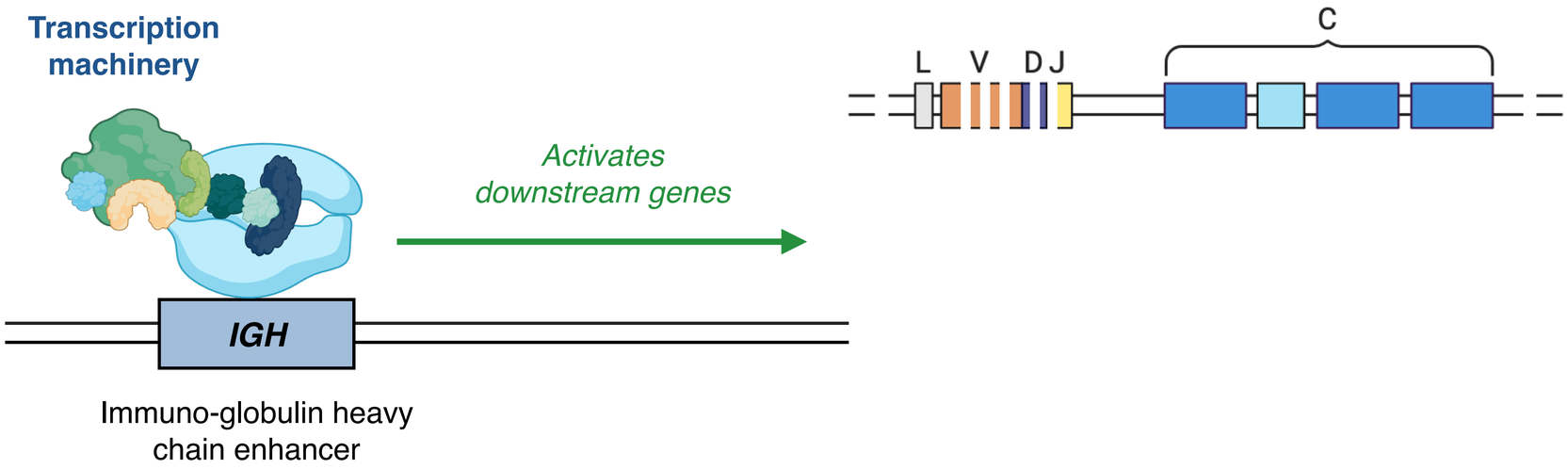

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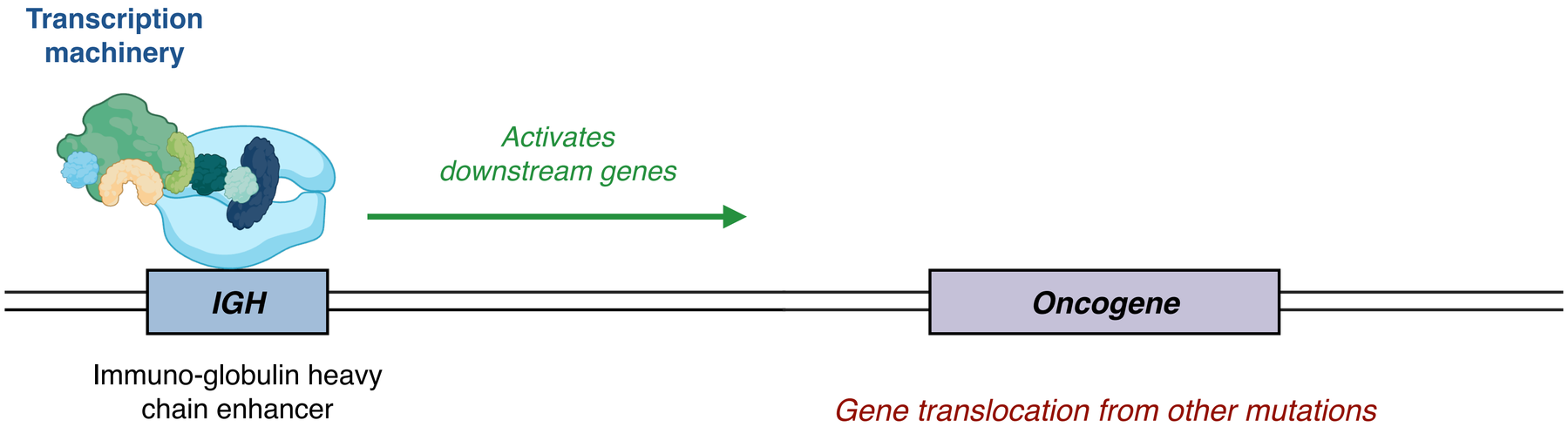

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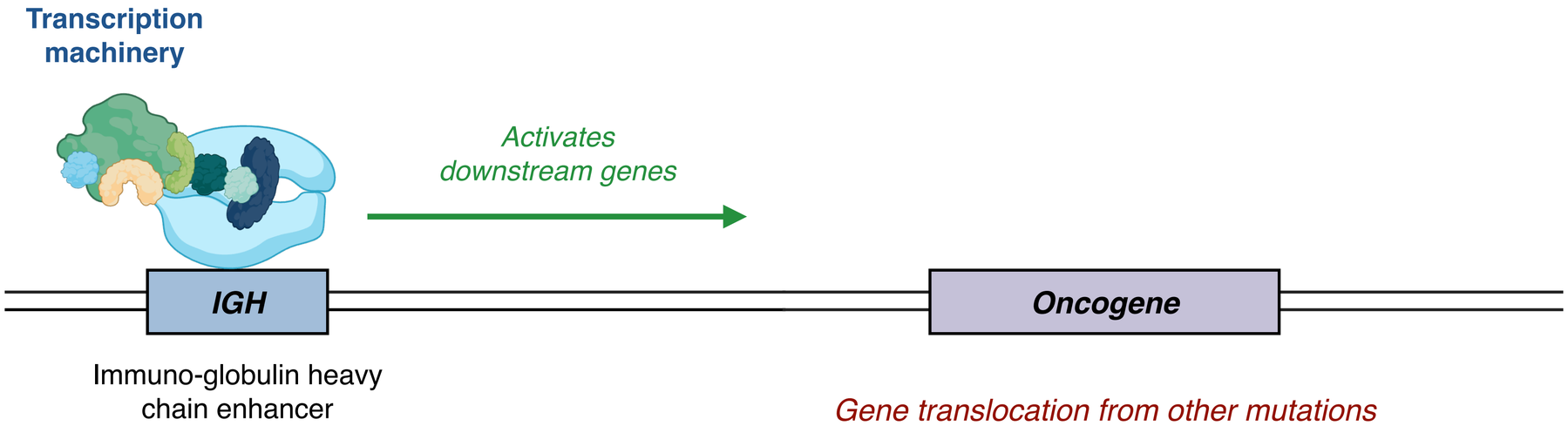

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What oncogene translocations generally result in myeloma?

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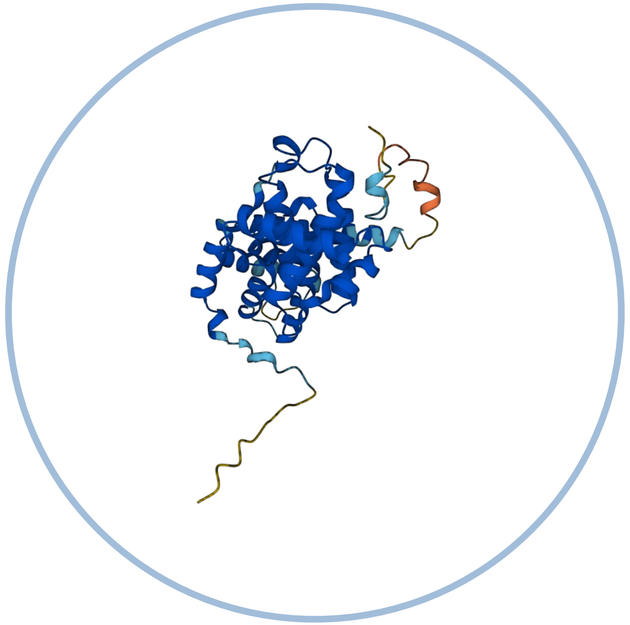
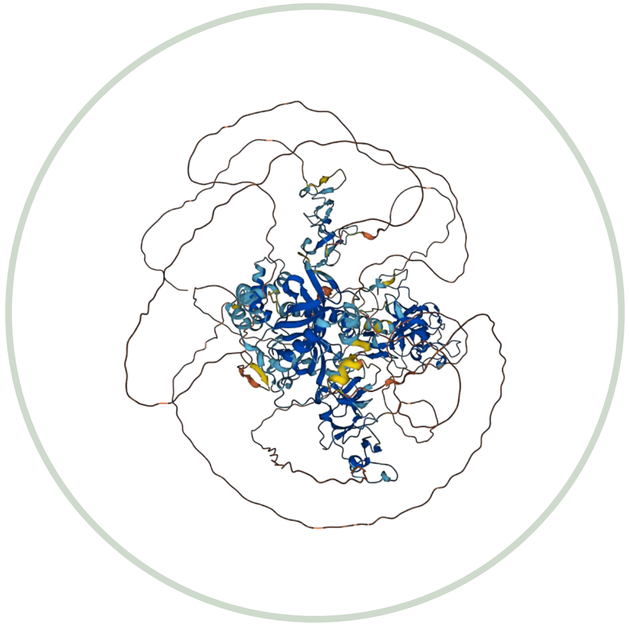


CCND1

Cyclin D1

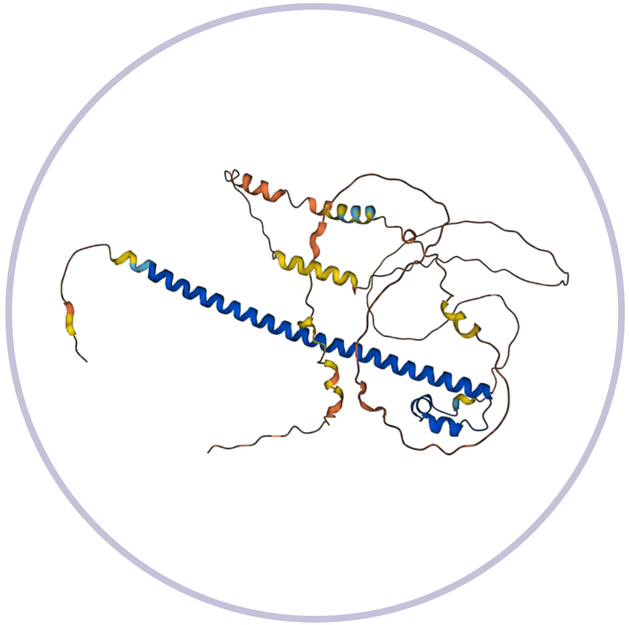
~20% of myelomas



MMSET

Multiple Myeloma SET domain protein

~15% of myelomas



MAF

c-MAF

~15% of myelomas

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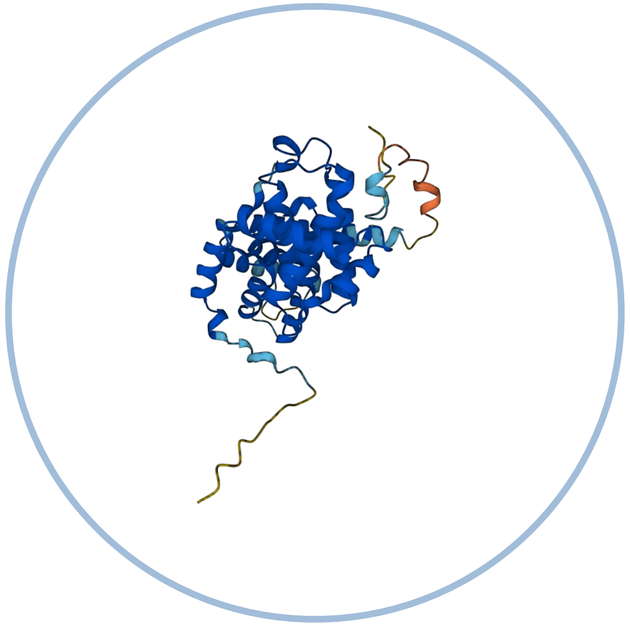

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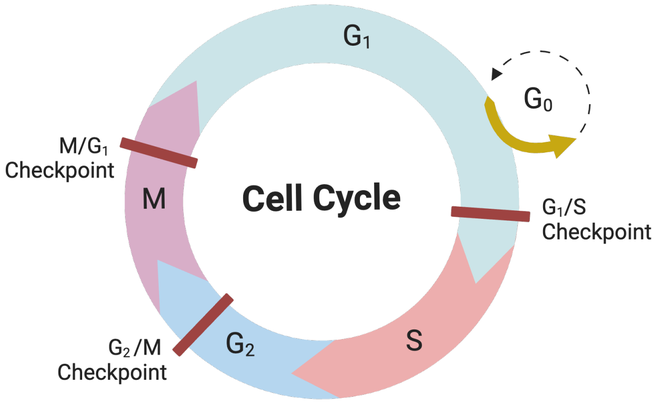
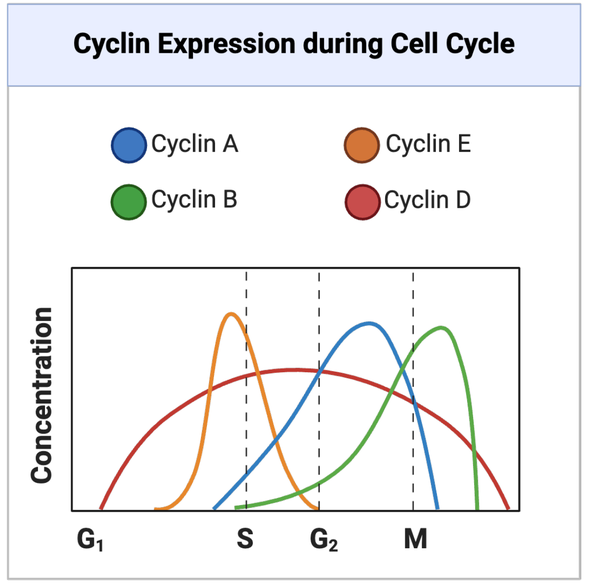
Morgan, G. J.; Walker, B. A.; Davies, F. E. *Nat Rev Cancer* **2012**, *12* (5), 335–348.

The role of cyclin D1 in multiple myeloma

The role of cyclin D1 in multiple myeloma



The process that governs cell division



Cyclins play a large role in regulating the cell cycle

CCDN1 → ***Faster cell cycle*** → ***Increased proliferation***

Bustany, S.; Cahu, J.; Guardiola, P.; Sola, B. *BMC Cancer* **2015**, *15* (1), 262.

Jiang, Y.; Zhang, C.; Lu, L. et. al. *Technol Cancer Res Treat* **2022**, *21*, 15330338211065252.

The role of cyclin D1 in multiple myeloma

Additional roles of CCND1

Bustany, S.; Cahu, J.; Guardiola, P.; Sola, B. *BMC Cancer* **2015**, *15* (1), 262.

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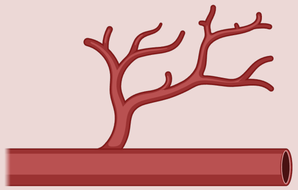
The role of cyclin D1 in multiple myeloma

Additional roles of CCND1

Interfacing with other transcription factors

ER-α ***AR***



Increased angiogenesis

Attraction of blood vessels and nutrients towards cancer

Bustany, S.; Cahu, J.; Guardiola, P.; Sola, B. *BMC Cancer* **2015**, *15* (1), 262.

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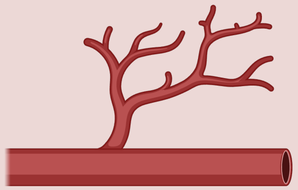
The role of cyclin D1 in multiple myeloma

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

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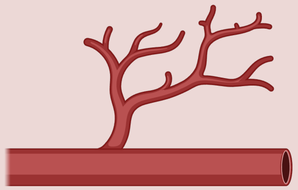

Increased angiogenesis

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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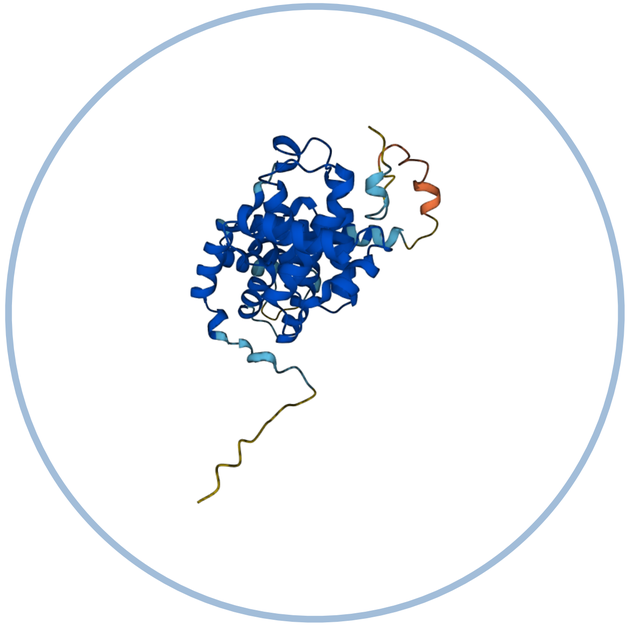
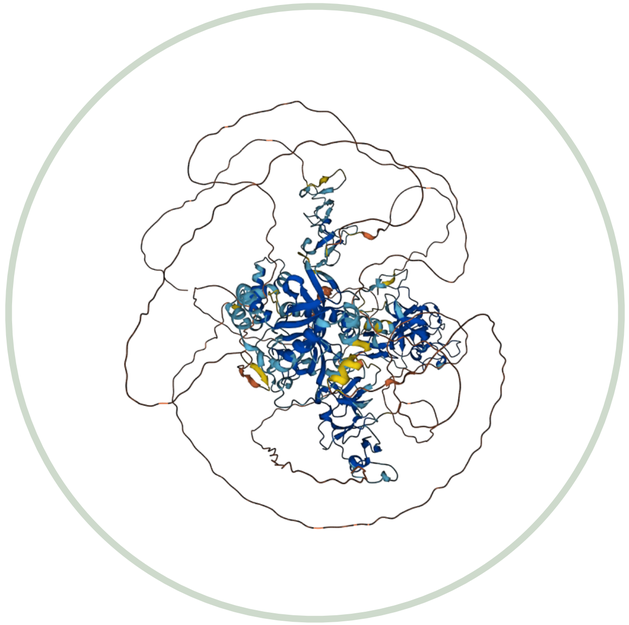


CCND1

Cyclin D1

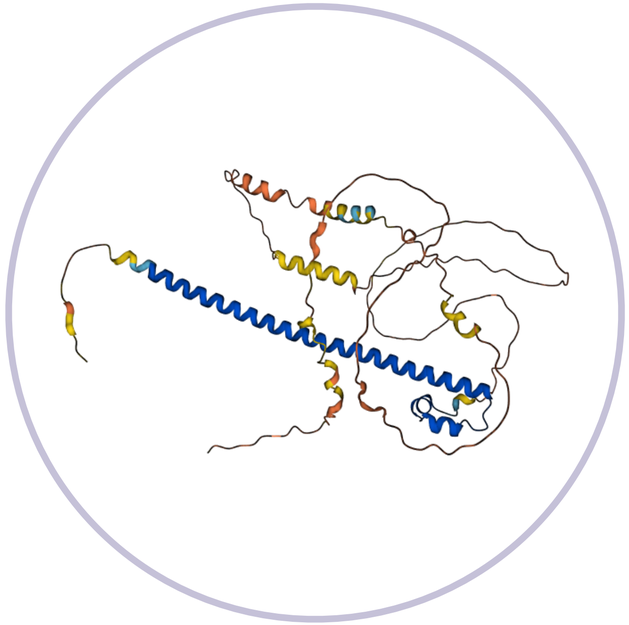
~20% of myelomas



MMSET

Multiple Myeloma SET domain protein

~15% of myelomas



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c-MAF

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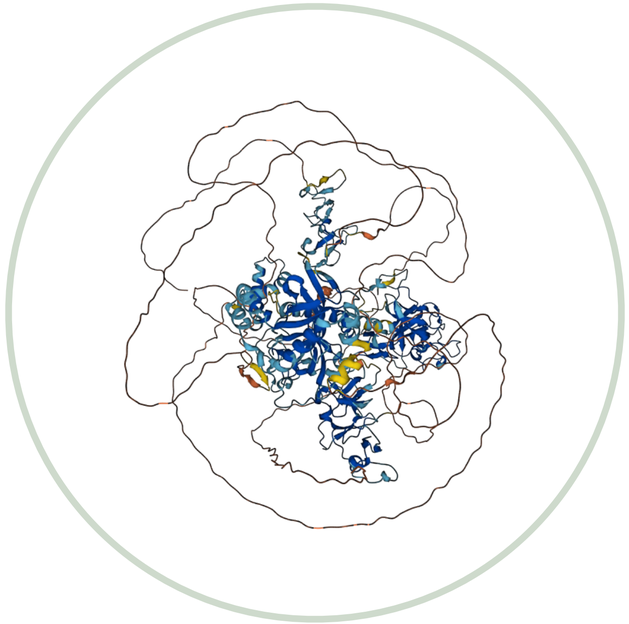

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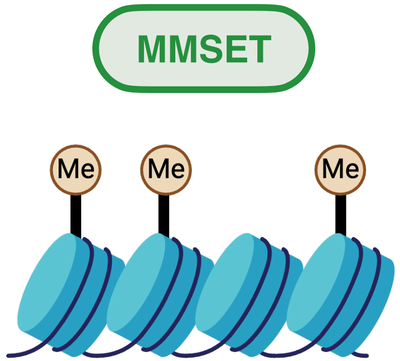
The role of MMSET in multiple myeloma



Histone methyltransferase

Azagra, A.; Cobaleda, C. *International Journal of Molecular Sciences* **2022**, *23* (19).

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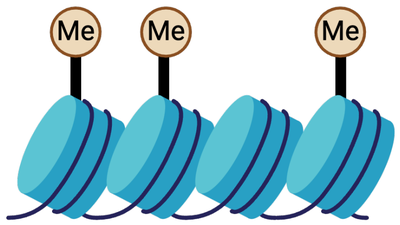

Histone methyltransferase

H3K36me2

Di-methylation of K36 on H3

Epigenetic remodeling

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

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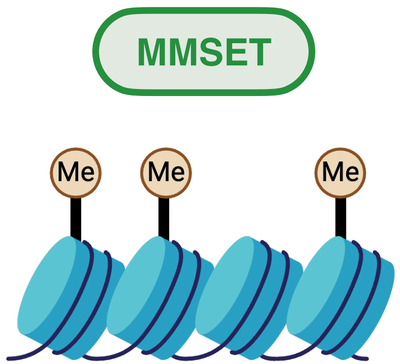

Histone methyltransferase

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*

Azagra, A.; Cobaleda, C. *International Journal of Molecular Sciences* **2022**, *23* (19).

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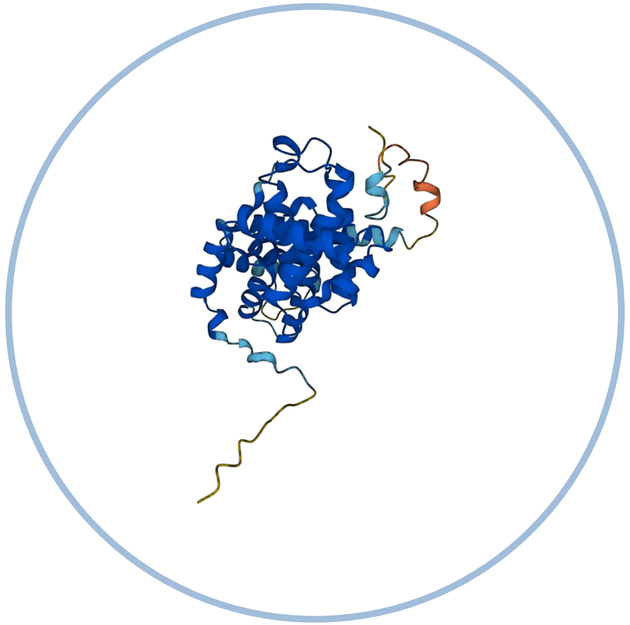

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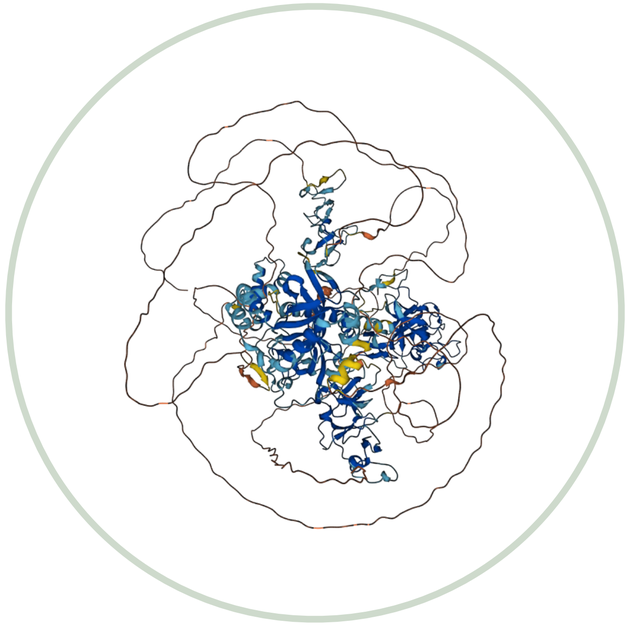

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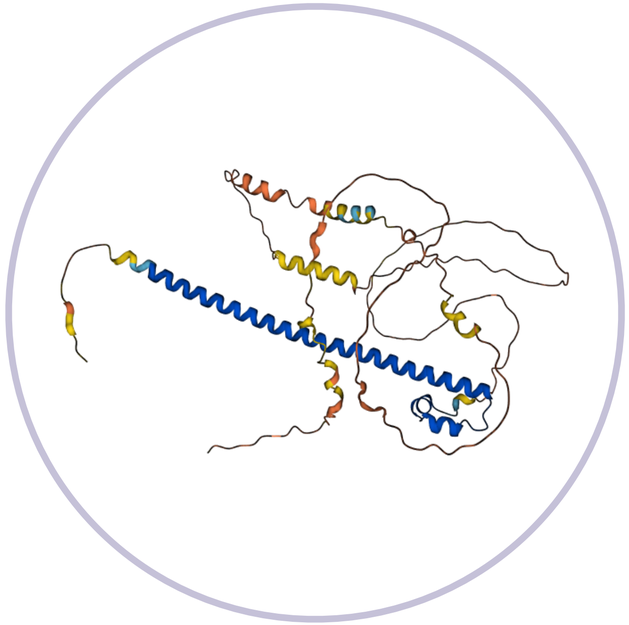

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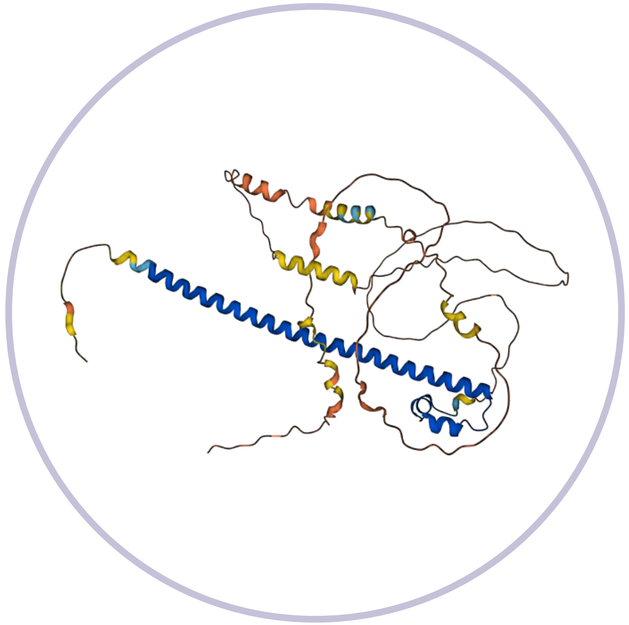

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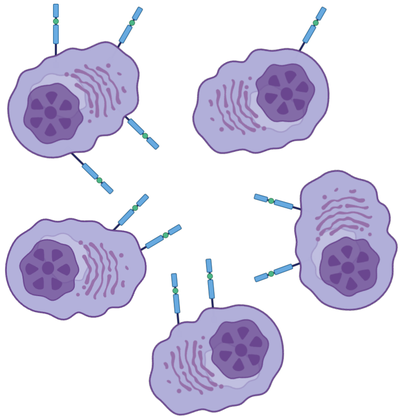
The role of MAF in multiple myeloma

c-MAF

Master regulator of mitogenic genes in plasma cells



Up-regulation of integrins:
Cell adhesion proteins

Gabryšová, L.; Alvarez-Martinez, M.; Luisier, R.; Cox, L. et. al. *Nat Immunol* **2018**, *19* (5), 497–507.

Jiang, Q.; Mao, H.; He, G.; Mao, X. *Cancer Letters* **2022**, *543*, 215791.

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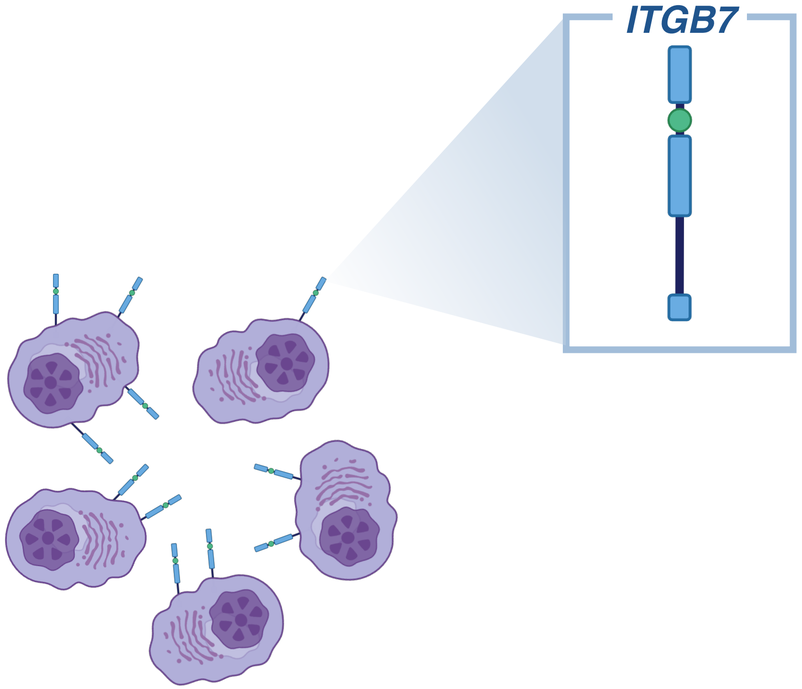

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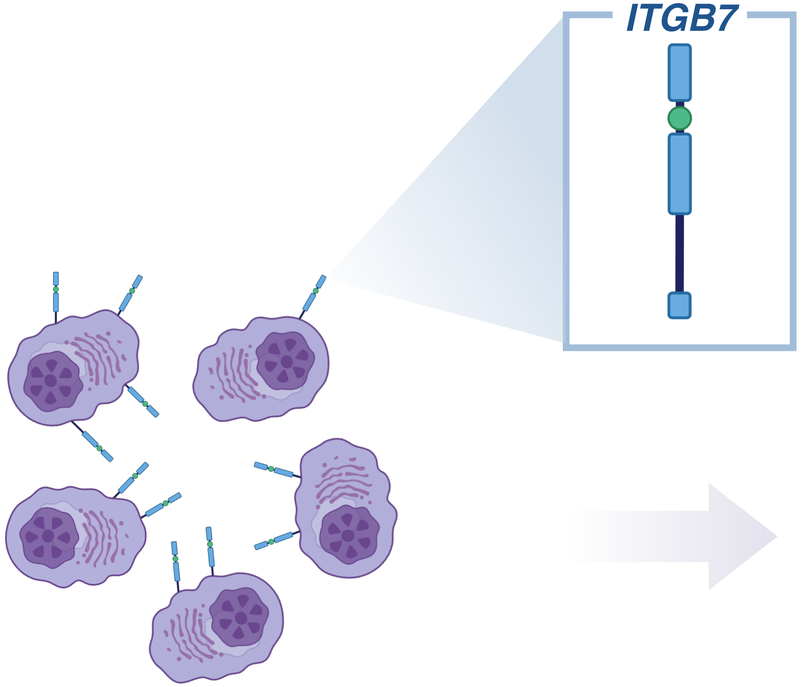

Up-regulation of integrins:
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Self adhesion

Extensive migration

Resistance to therapies

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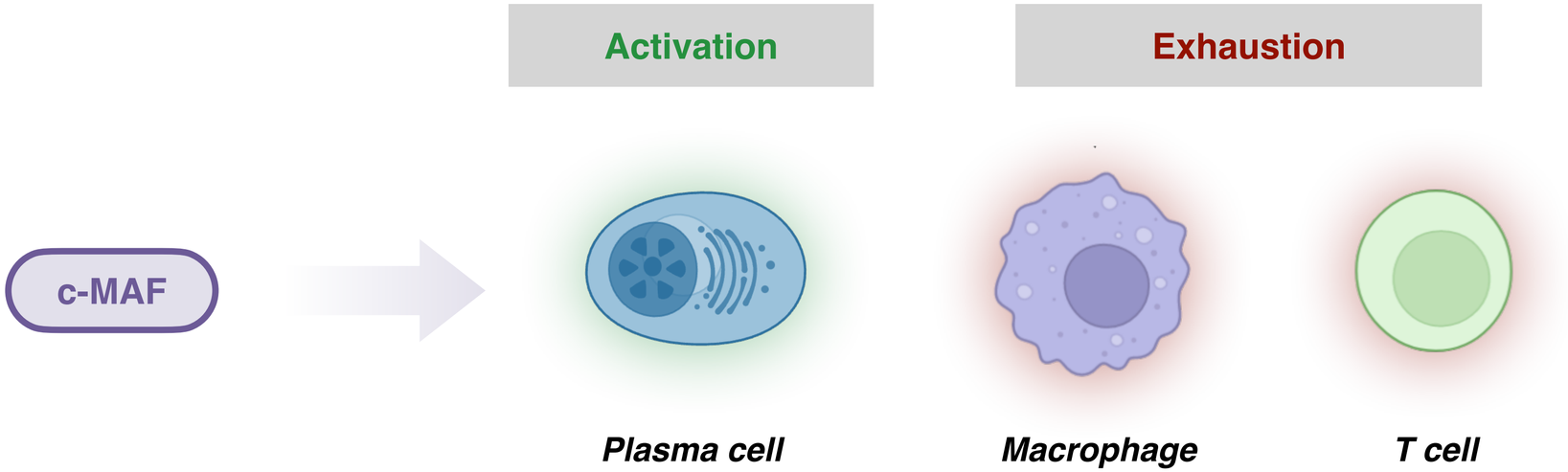

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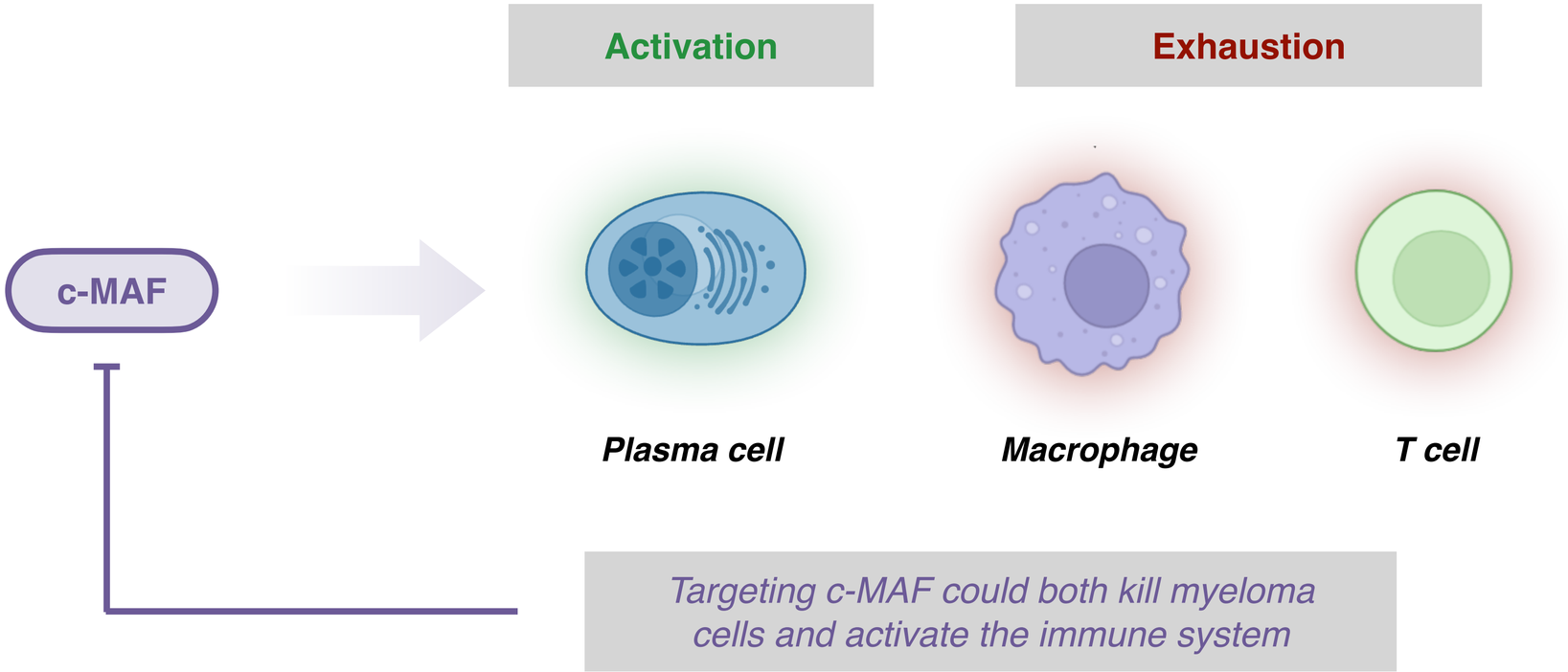

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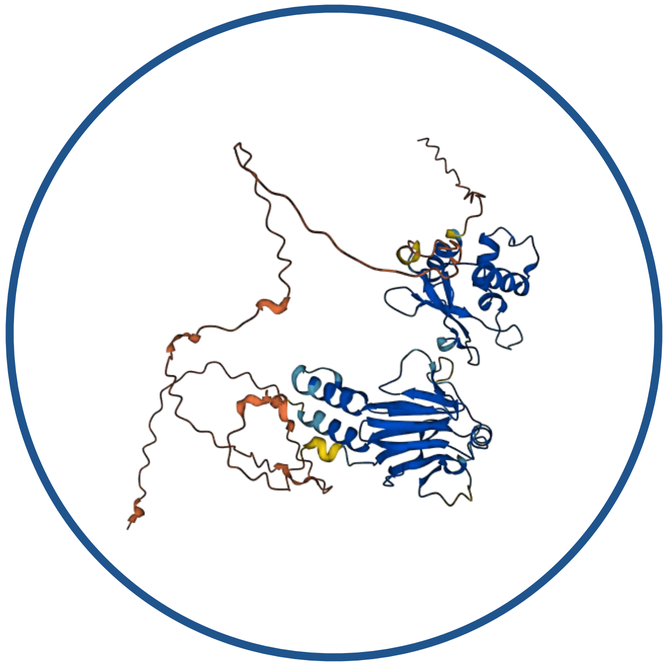
IRF4 is up-regulated in multiple myeloma



IRF4

Interferon regulatory factor 4

Can be up-regulated in a variety of different ways

Kumar, S. K.; Rajkumar, V.; et. al. *Nat Rev Dis Primers* **2017**, *3* (1), 1–20.

Man, K.; Gabriel, S. S.; Liao, Y.; Gloury, R.; et. al. *Immunity* **2017**, *47* (6), 1129-1141.e5.

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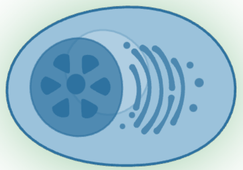
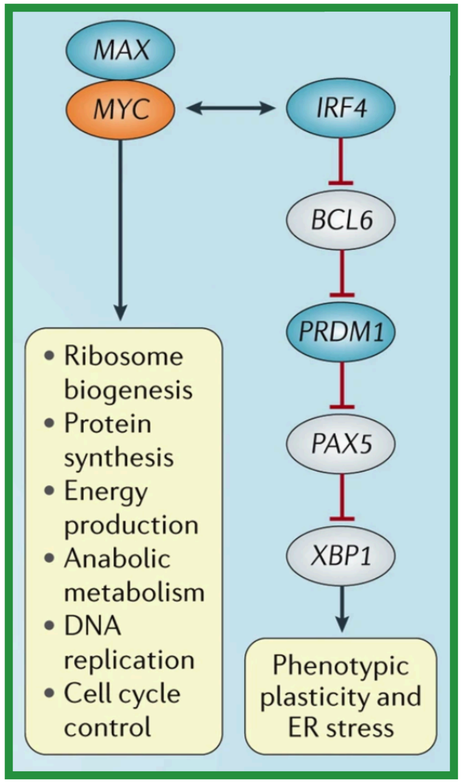


Plasma cell



Pro-growth signals

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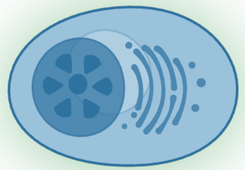

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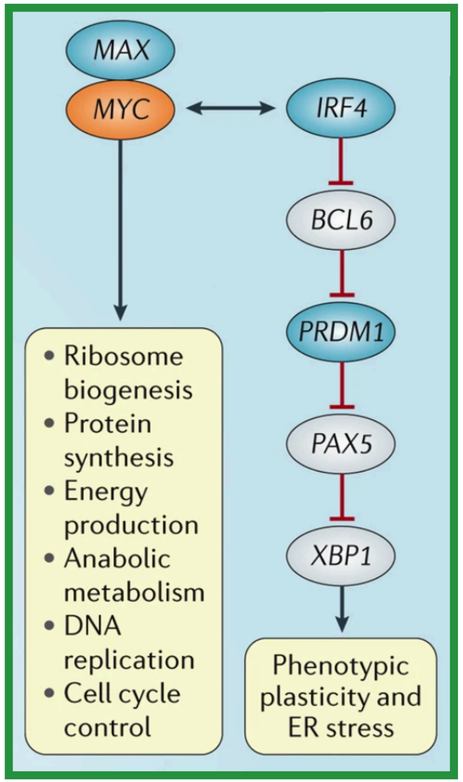

Pro-growth signals

T cells

PD-1 **TIM-3**

TIGIT **LAG3**

Exhaustion signals

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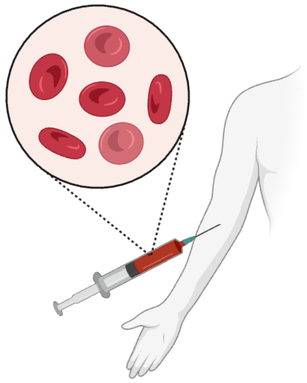
3: Treatment

Initial treatment often includes stem cell transplant



Autologous stem cell transplant

Bone marrow fully depleted, replaced by ones own stem cells

Types of treatment for multiple myeloma

1. IMiDs

2. Proteasome inhibitors

3. Dexamethasone

4. Novel therapeutics

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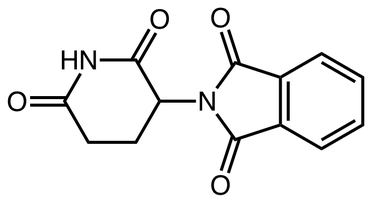
Immunomodulatory Imide Drugs: Molecular Glues that Bind Cereblon

Immunomodulatory Imide Drugs (IMiDs)



Thalidomide

Morning sickness (1957)

1960s

Thalidomide induces Birth Defects

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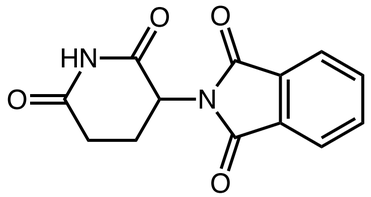

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Cancer treatment (1991)

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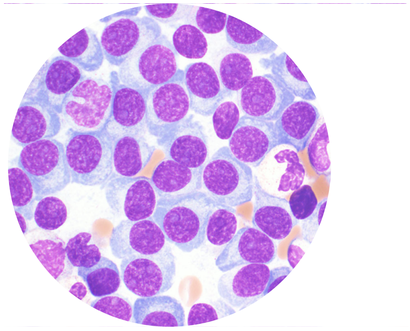

Multiple Myeloma

B cell cancer

Celgene

Bristol Myers Squibb

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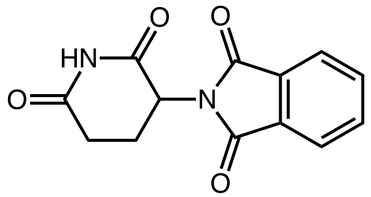

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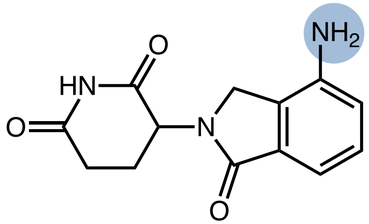
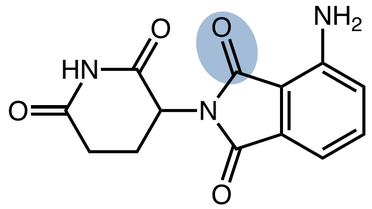


Lenalidomide

$10.1 billion in sales (2022)

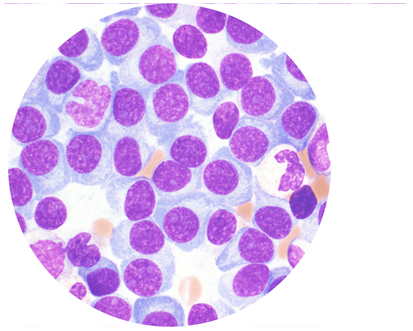


Pomalidomide

$3.5 billion in sales (2022)

1960s

Thalidomide induces Birth Defects



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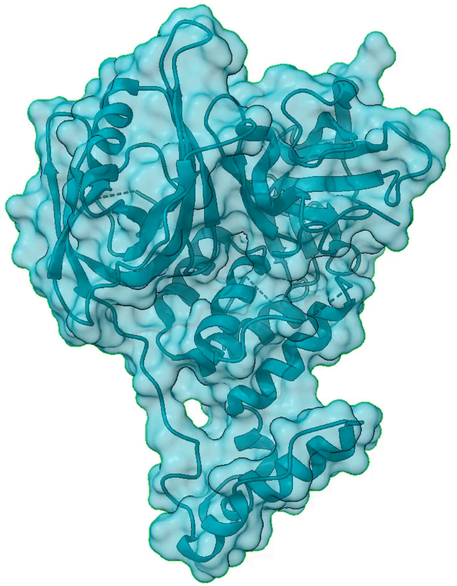
Immunomodulatory Imide Drugs: Molecular Glues that Bind Cereblon

Cereblon



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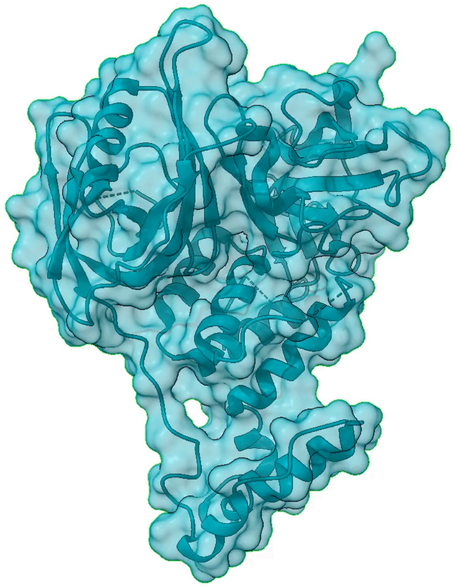
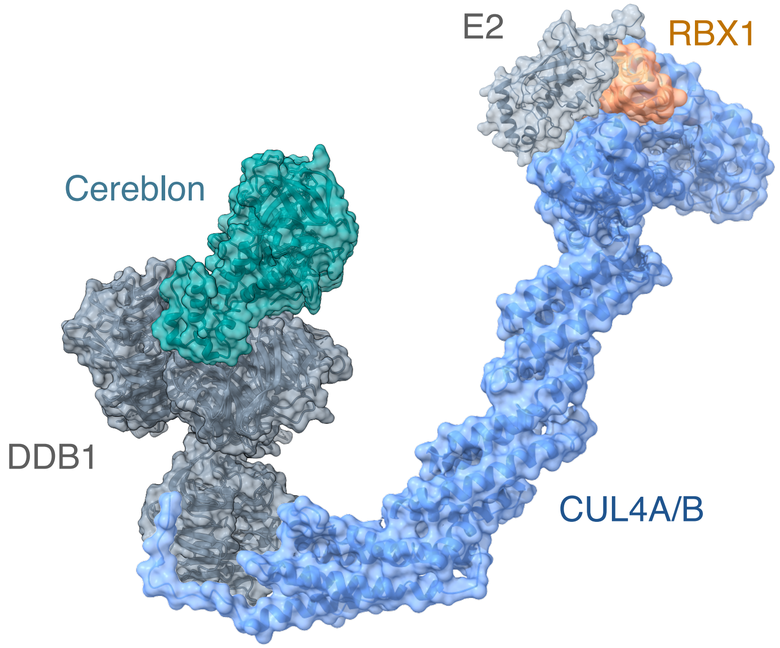


Cereblon E3 ligase complex



Cereblon is an adaptor for the Cullin Ring E3 Ligase Complex

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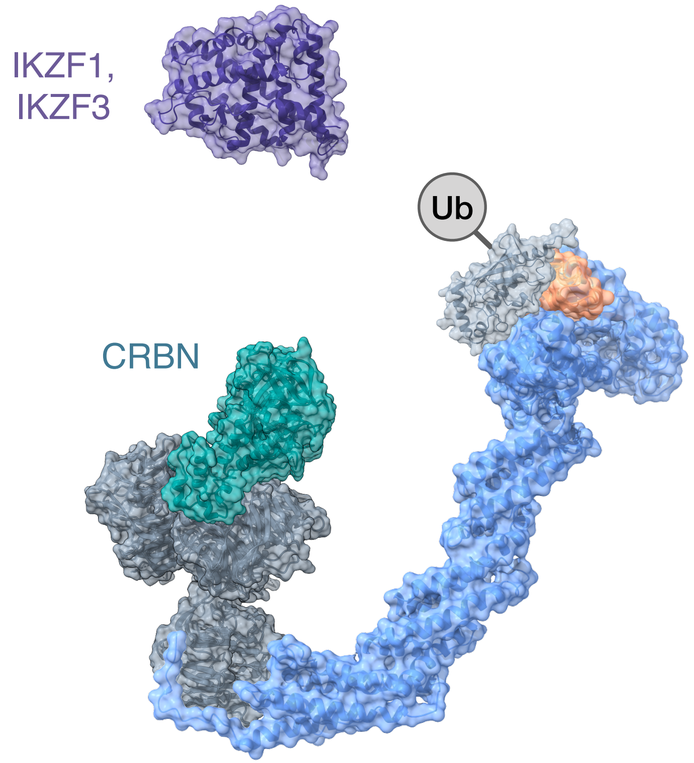
IMiDs function as Molecular Glues to Induce Targeted Protein Degradation

Mechanism of Action



Cereblon E3 ligase complex

Krönke, J. et al. *Science* **2013**, *343*, 301.
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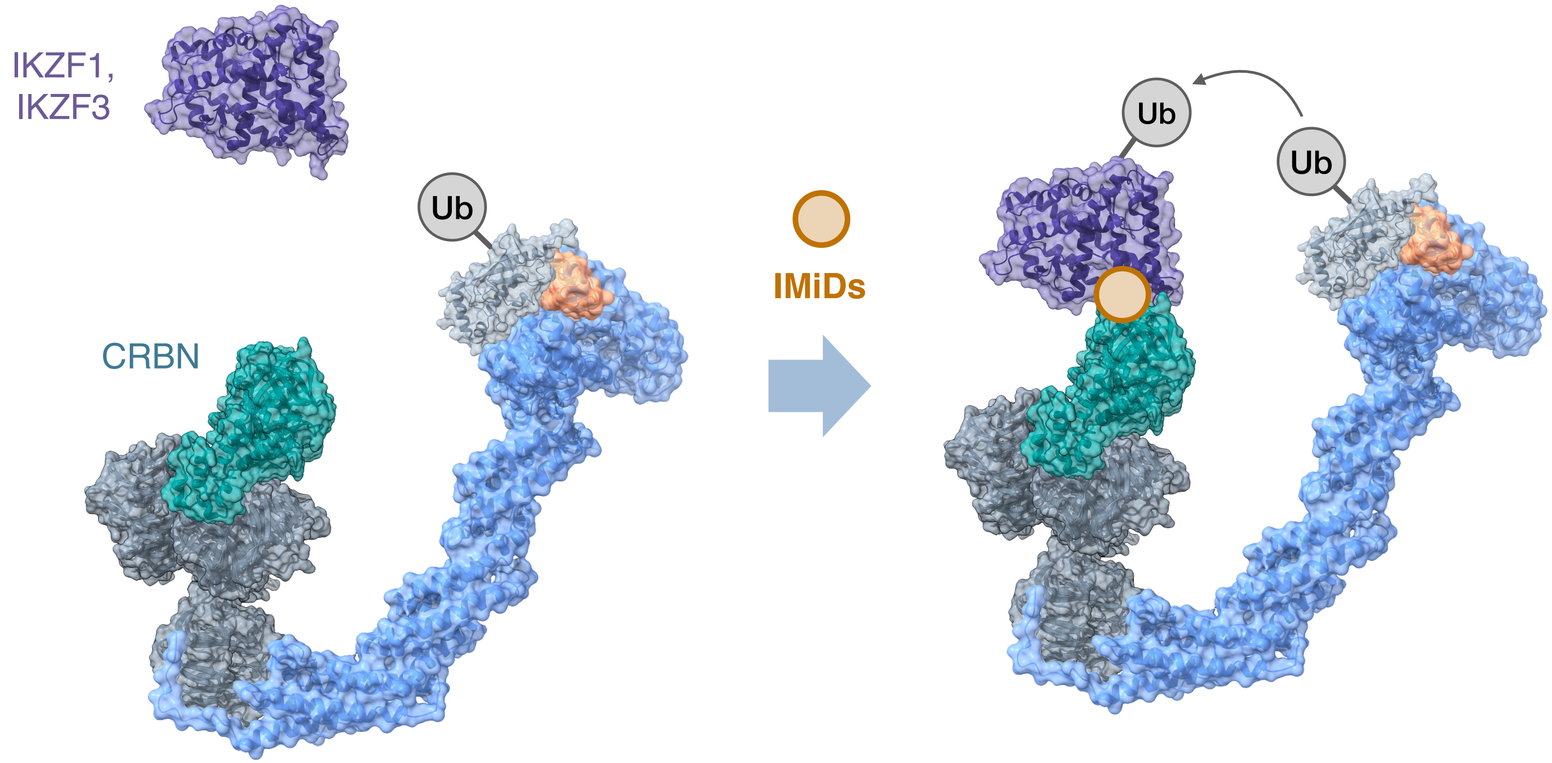

Cereblon E3 ligase complex

Ternary complex formation

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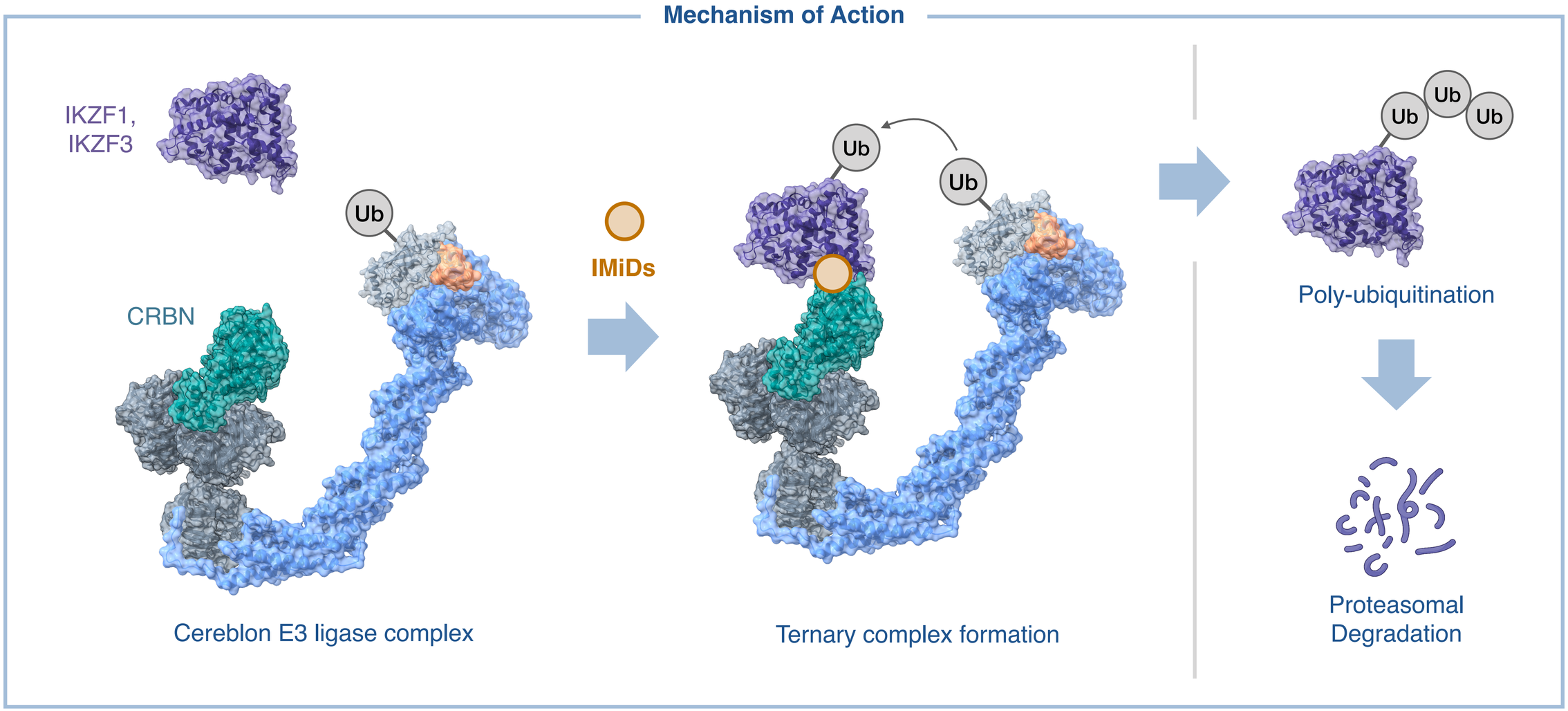

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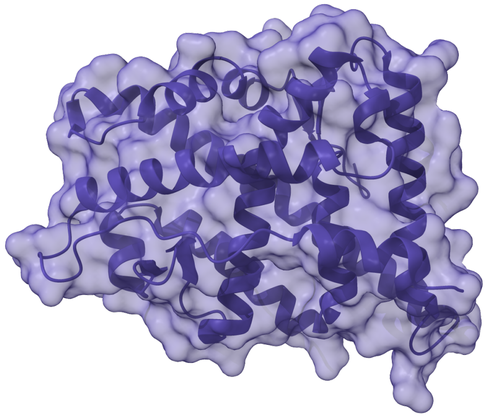
What is the consequence of degrading IKZF1 and IKZF3?



Ikaros / Aiolos

IKZF1 / IKZF3

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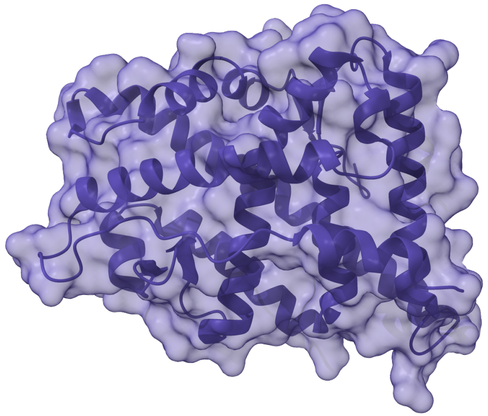
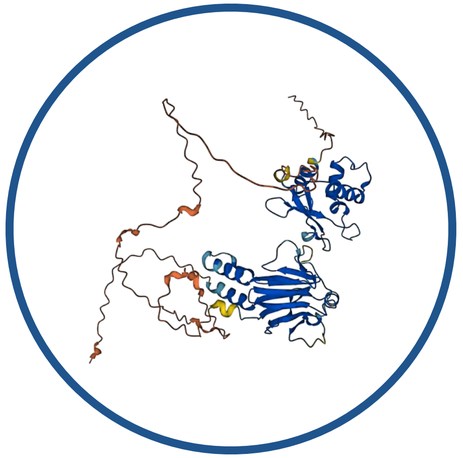


Ikaros / Aiolos

IKZF1 / IKZF3

Transcriptionally up-regulate



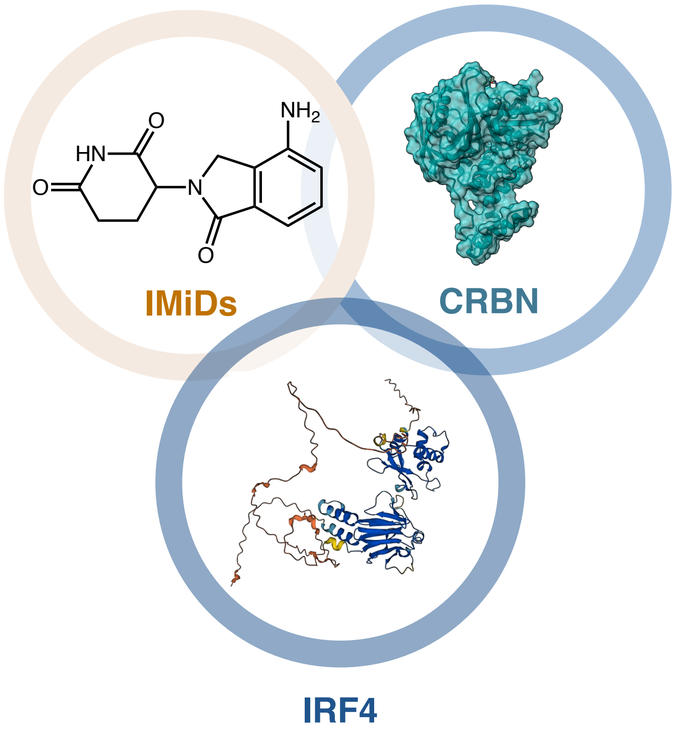
IRF4

Myeloma driver

Drives T-cell exhaustion

Krönke, J. et al. *Science* **2013**, *343*, 301.
Lu, G. et al. *Science* **2013**, *343*, 305.

Therapeutic relevance of IRF4 inhibition



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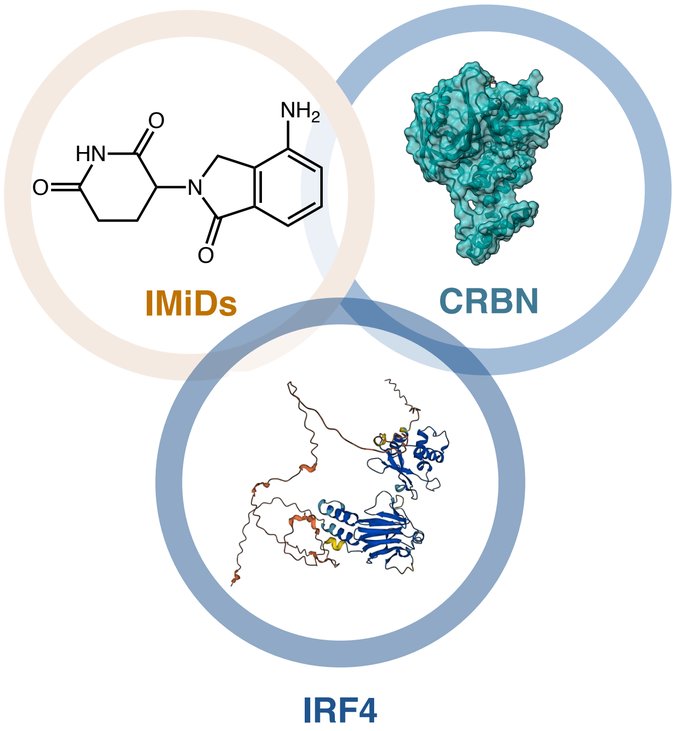
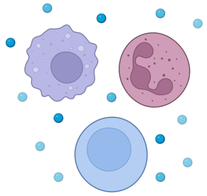


Myeloma Cell Death

- Apoptosis
- Growth Inhibition

Immune cell activation



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

Krönke, J. et al. *Science* **2013**, *343*, 301.
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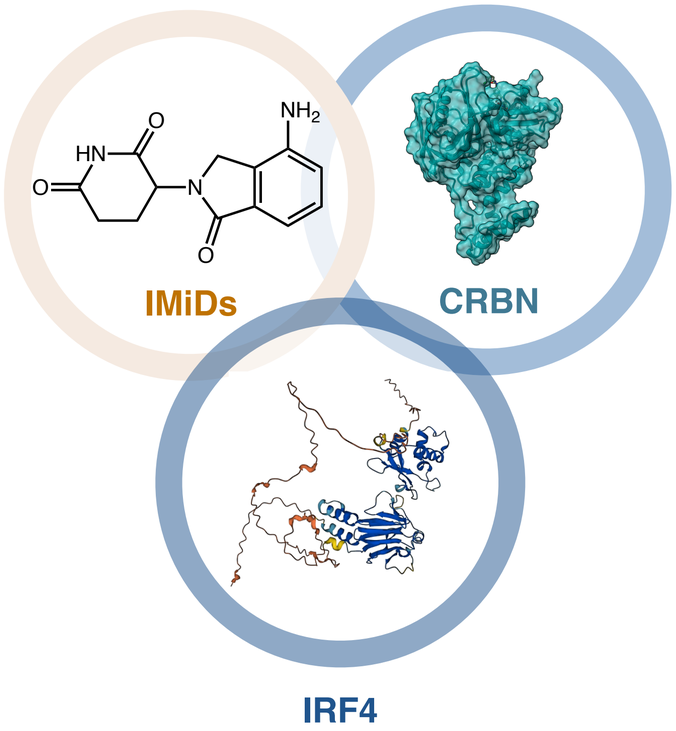

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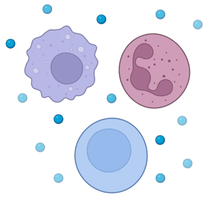
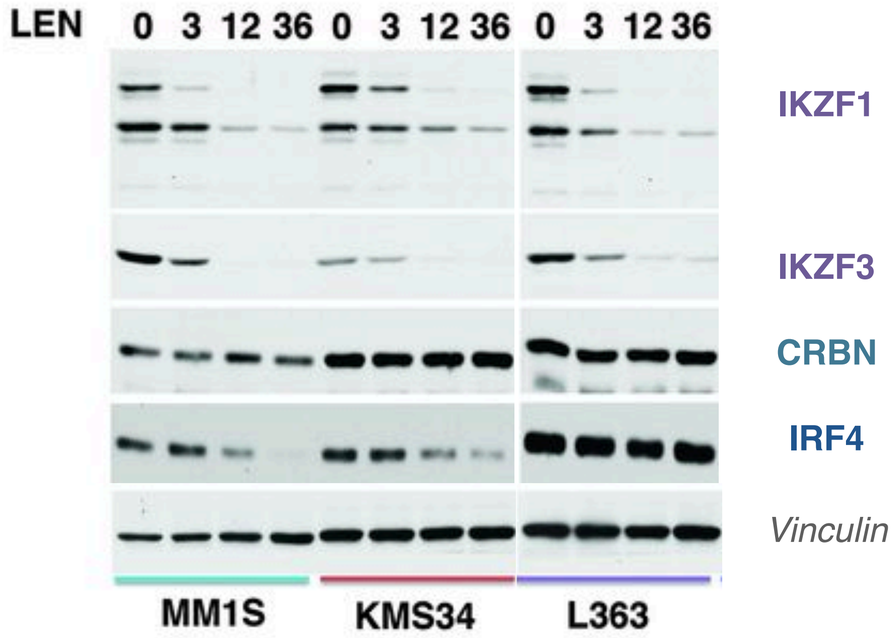


- T cell and NK cell activation
- IL-2 and IFN-γ secretion

How important is IRF4 for IMiD mediated cell death?

Krönke, J. et al. *Science* **2013**, *343*, 301.
Lu, G. et al. *Science* **2013**, *343*, 305.

IMiDs function as Molecular Glues to Induce Targeted Protein Degradation



Len-sensitive

Lu, G. et al. *Science* **2013**, *343*, 305.

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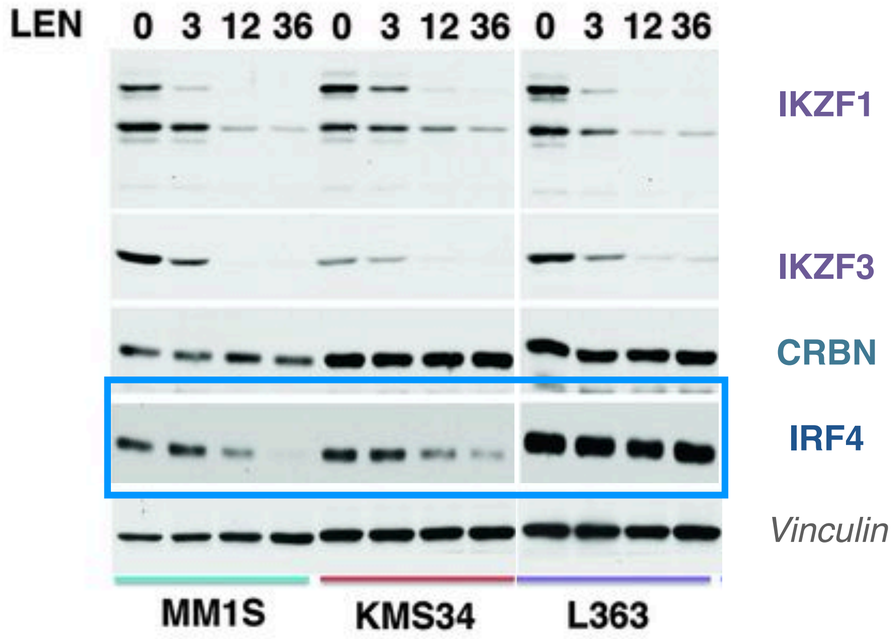

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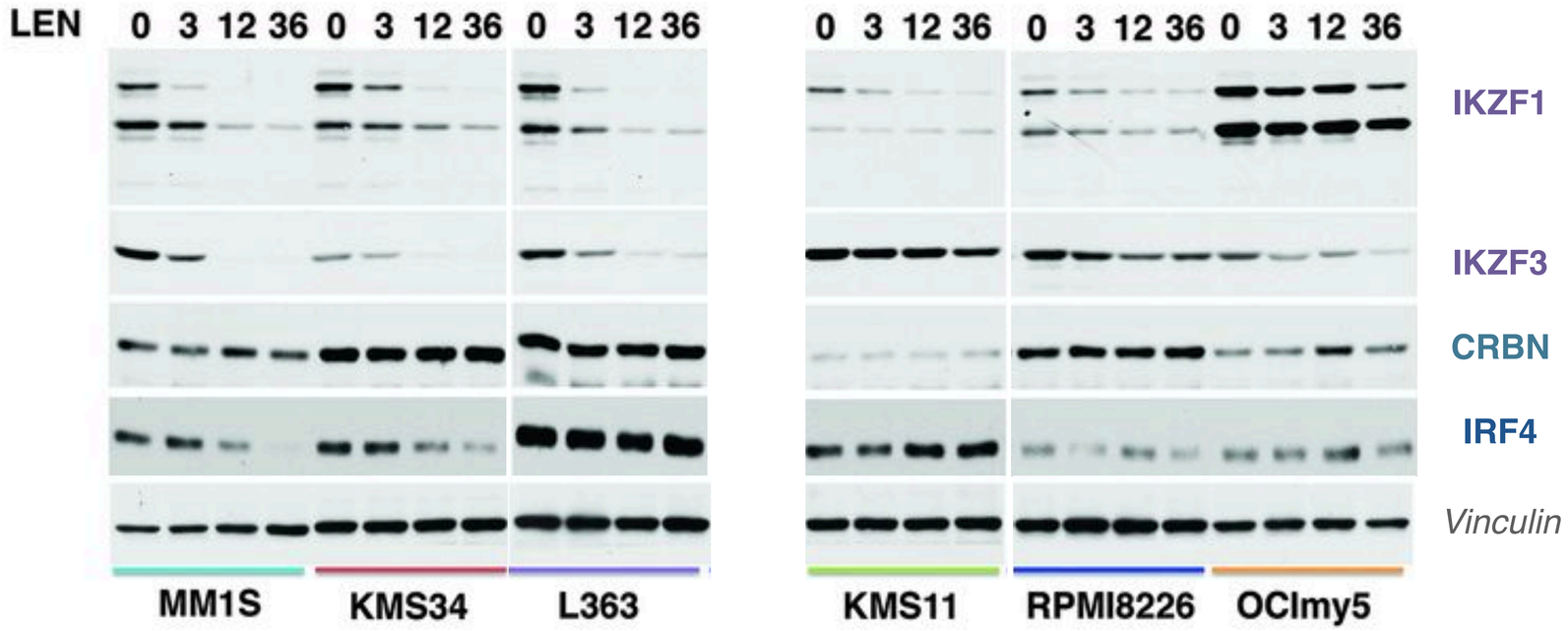
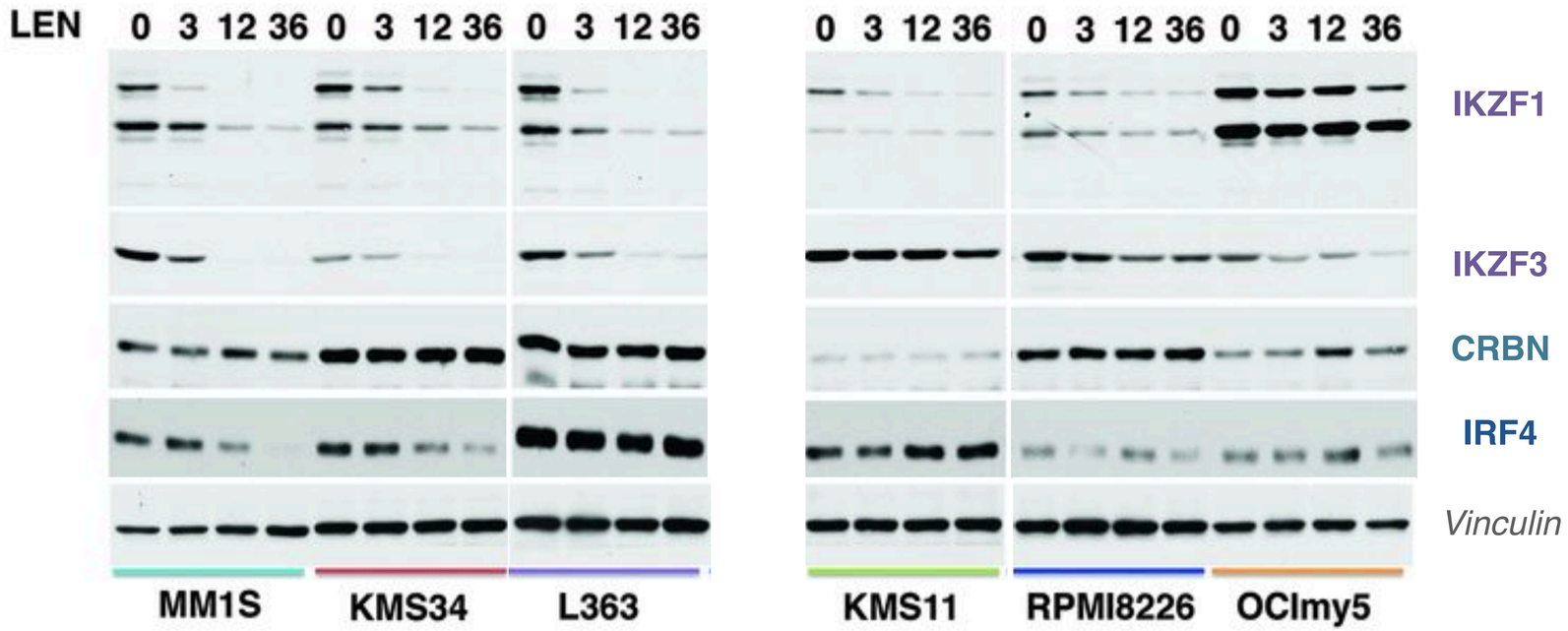


Len-sensitive ***Len-Resistant***

Lu, G. et al. *Science* **2013**, *343*, 305.

IMiDs function as Molecular Glues to Induce Targeted Protein Degradation

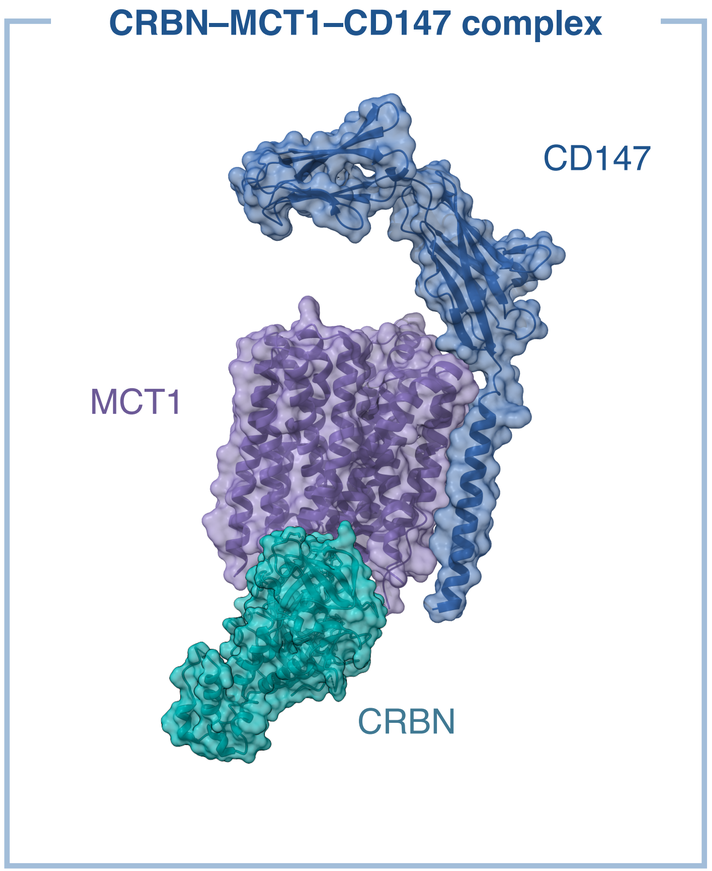


Len-sensitive ***Len-Resistant***

"…antiproliferative effects of this drug involves at least one target other than IRF4."

Lu, G. et al. *Science* **2013**, *343*, 305.

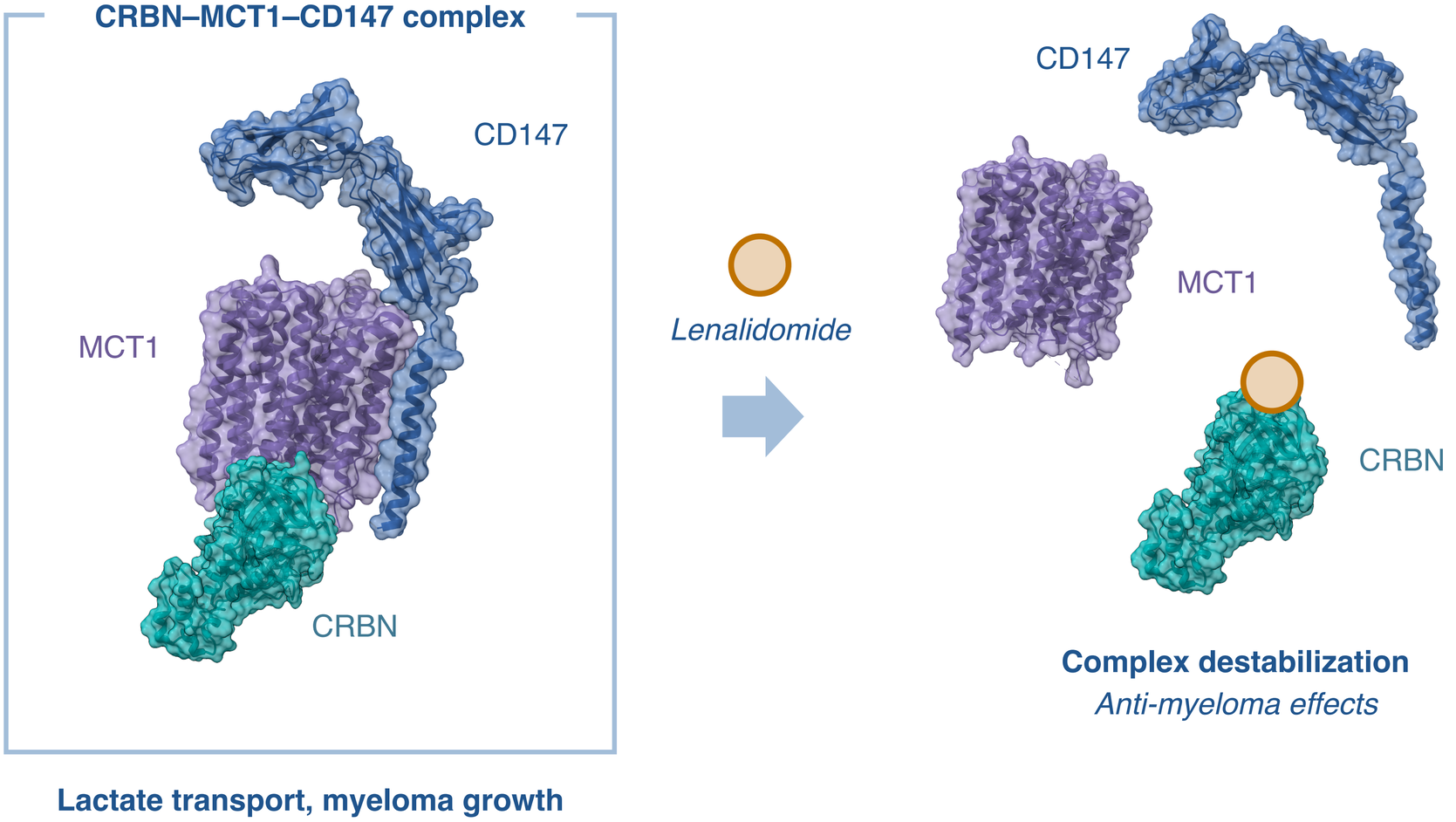
Additional mechanisms beyond IRF4



Lactate transport, myeloma growth

Eichner, R. et. al. *Nature Medicine*, **2016**, *22*, 735–743.

Additional mechanisms beyond IRF4



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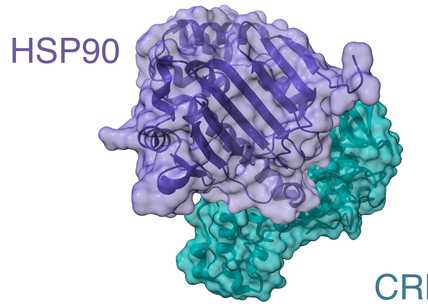
Additional mechanisms beyond IRF4

CRBN–HSP90 complex

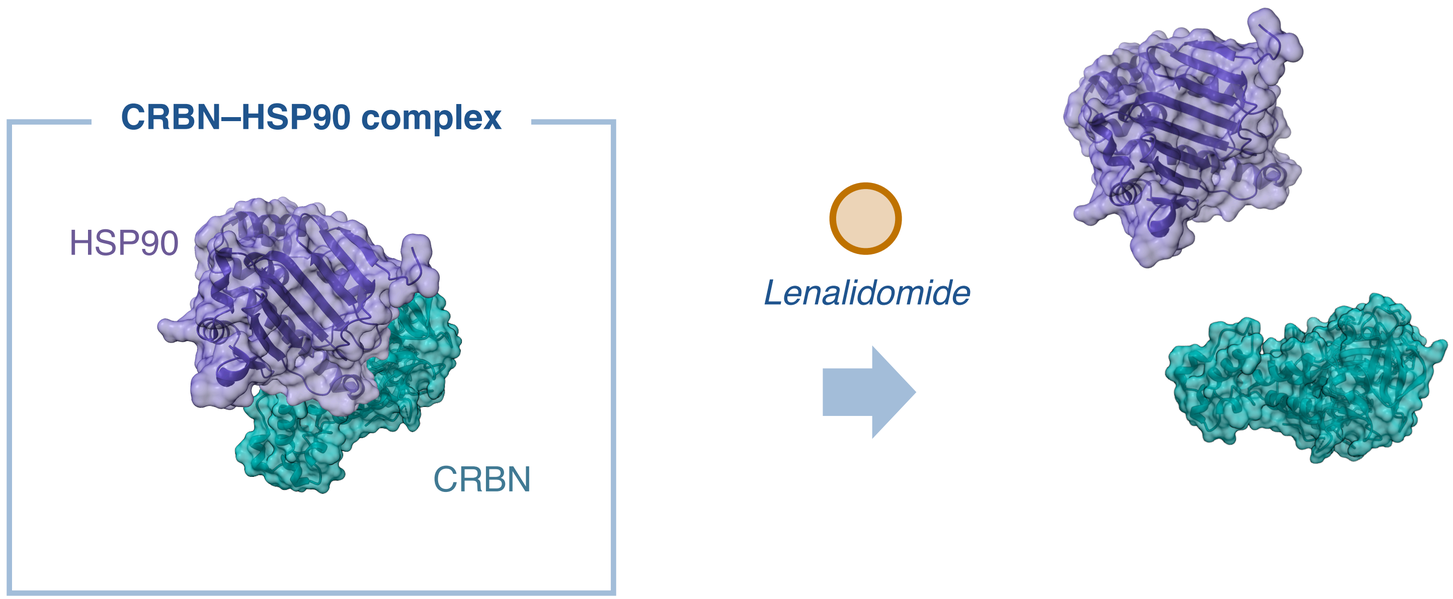


Co-chaperoning complex

Helps stabilize membrane proteins

Heider, M.; Eichner, R.; Stroh, J.; Morath, V.; Kuisl, A.; et. al. *Mol Cell* **2021**, *81* (6), 1170-1186.e10.

Additional mechanisms beyond IRF4



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Complex destabilization

Heider, M.; Eichner, R.; Stroh, J.; Morath, V.; Kuisl, A.; et. al. *Mol Cell* **2021**, *81* (6), 1170-1186.e10.

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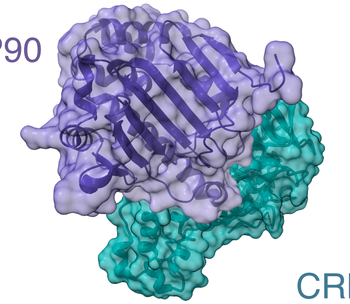
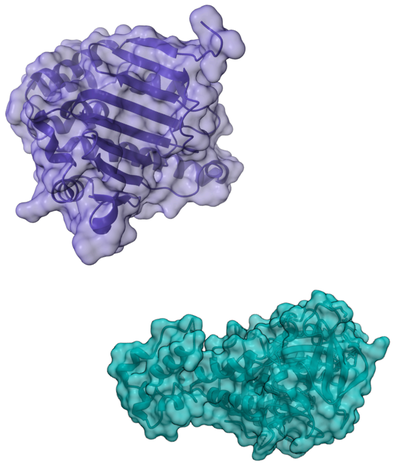


Co-chaperoning complex

Helps stabilize membrane proteins

Lenalidomide



Complex destabilization

Misfolded

LAT1, CD98, etc.

Destabilization of chaperone targets

Anti-myeloma effects

Heider, M.; Eichner, R.; Stroh, J.; Morath, V.; Kuisl, A.; et. al. *Mol Cell* **2021**, *81* (6), 1170-1186.e10.

Types of treatment for multiple myeloma

1. IMiDs

2. Proteasome inhibitors

3. Dexamethasone

4. Novel therapeutics

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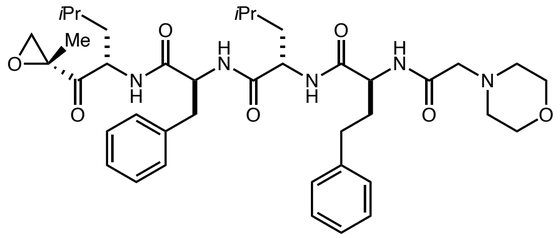
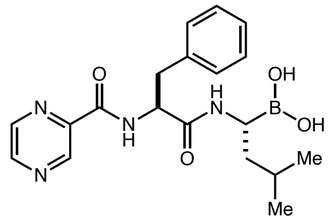
Proteasome inhibitors

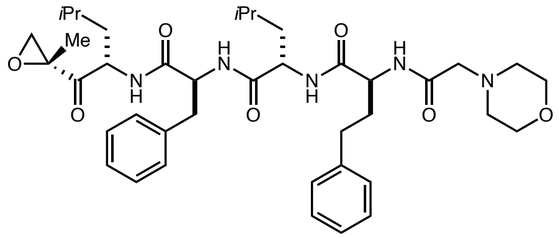


Carfilzomib



Bortezomib

Proteasome inhibitors



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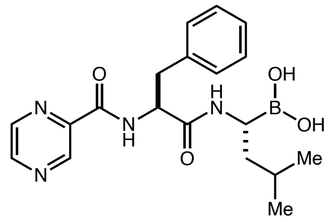
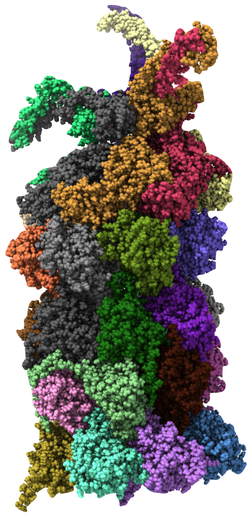


Bortezomib

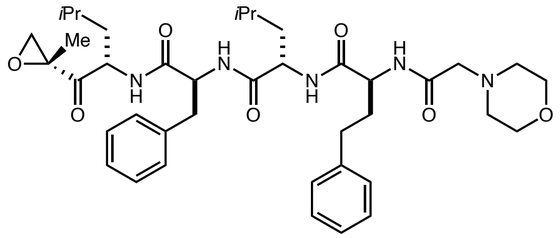


26S Proteasome

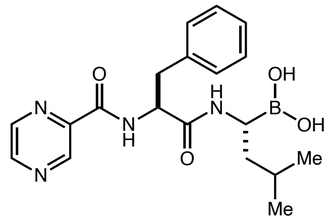
How the majority of proteins are degraded

Curran, M. P.; McKeage, K. *Drugs* **2009**, *69* (7), 859–888.

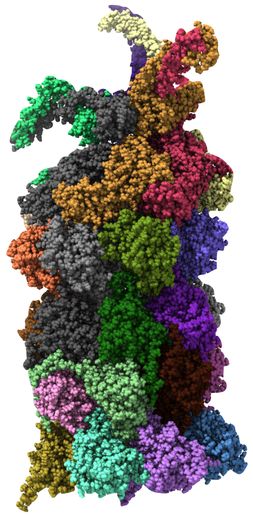
Proteasome inhibitors



Carfilzomib



Bortezomib



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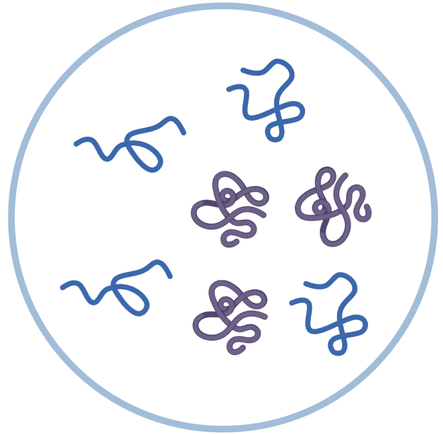


Misfolded proteins

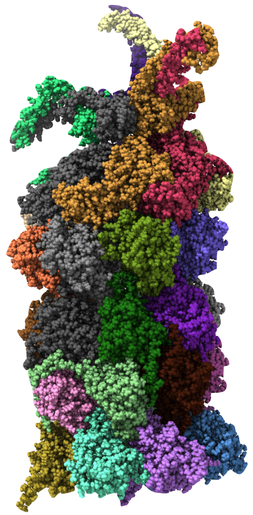
CCDN1

Particularly prone to apoptosis

Curran, M. P.; McKeage, K. *Drugs* **2009**, *69* (7), 859–888.

Proteasome inhibitors

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



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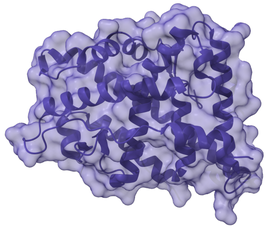
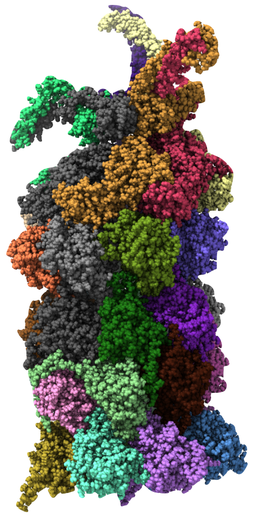


IKZF1/3



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How the majority of proteins are degraded

Proteasomal degradation

Proteasome inhibitors

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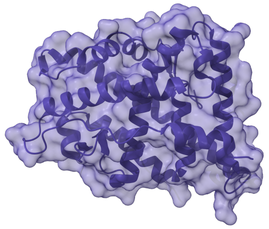

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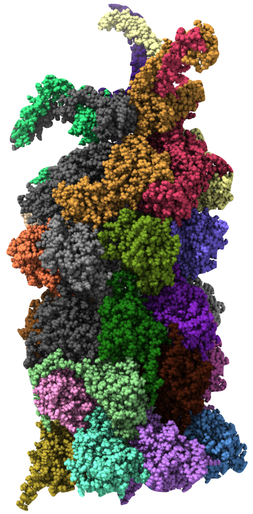

26S Proteasome

How the majority of proteins are degraded

Proteasomal degradation

IMiDs + proteasome inhibitors should be theoretically **incompatible**

IMiDs and proteasome inhibitors exhibit synergy in treating multiple myeloma

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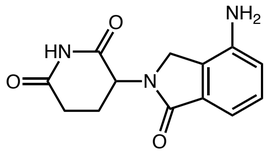
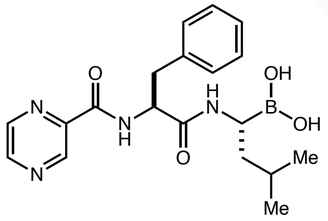
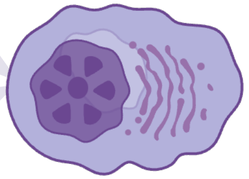


Lenalidomide



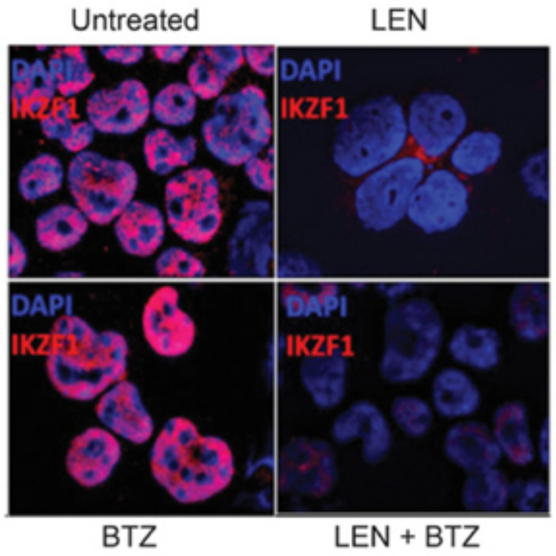
Bortezomib



Increased apoptosis
Compared to monotherapy

Ganesan, S.; Palani, H. K.; Balasundaram, N.; David, S.; Devasia, A. J.; George, B.; Mathews, V. *Mol Cancer Res* **2020**, *18* (4), 529–536.

IMiDs and proteasome inhibitors exhibit synergy in treating multiple myeloma



IKZF1 degradation is maintained upon co-treatment

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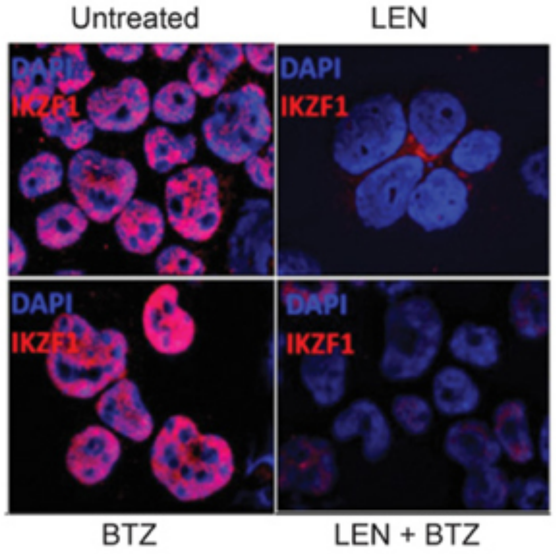

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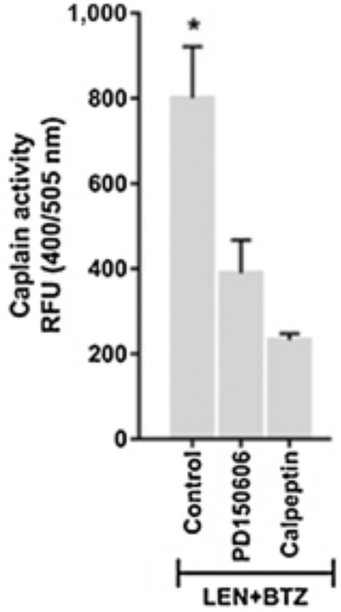

Degradation is dependent on ***calpain proteases***

Ganesan, S.; Palani, H. K.; Balasundaram, N.; David, S.; Devasia, A. J.; George, B.; Mathews, V. *Mol Cancer Res* **2020**, *18* (4), 529–536.

Dexamethasone also exhibits synergy with IMiDs and proteasome inhibitors

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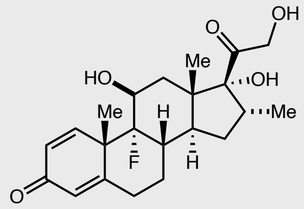
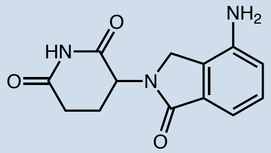


Dexamethasone

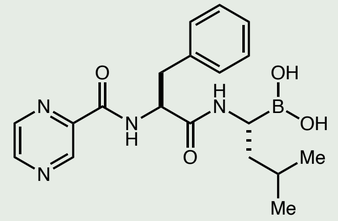
Immunosuppressant



Lenalidomide

Proteasomal degrader

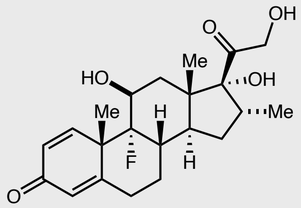
Immuno stimulant



Bortezomib

Proteasome inhibitor

Dexamethasone also exhibits synergy with IMiDs and proteasome inhibitors



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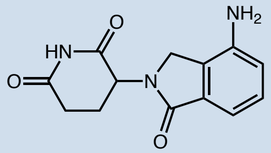
Immunosuppressant



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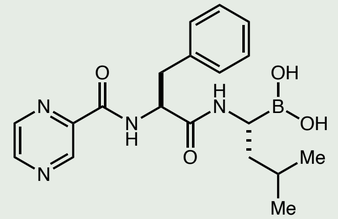

Bortezomib

Proteasome inhibitor

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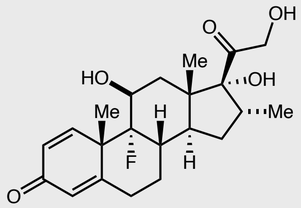
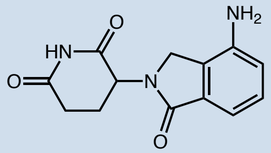


Dexamethasone

Immunosuppressant



Lenalidomide

Proteasomal degrader

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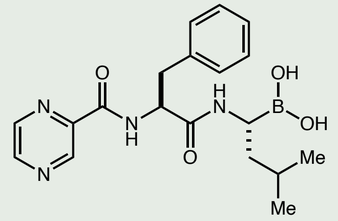

Bortezomib

Proteasome inhibitor

Synergistic effect still seen despite possible therapeutic conflicts

Types of treatment for multiple myeloma

1. IMiDs

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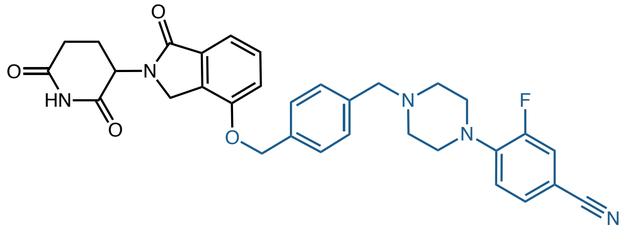
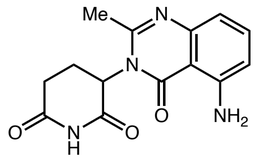
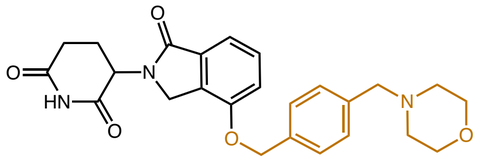
CeLMODs: Next generation IMiDs



Mezigdomide



Avadomide

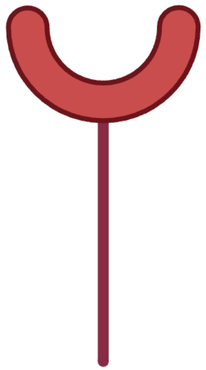


Iberdomide

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

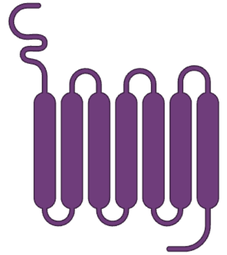
CD47

Monoclonal antibody

CD138

Antibody drug conjugate

GPR5D



Monoclonal antibody

CAR-T

Questions