Mass General Brigham
Mass General Cancer Center

The TEMPI Syndrome

EMORY UNIVERSITY

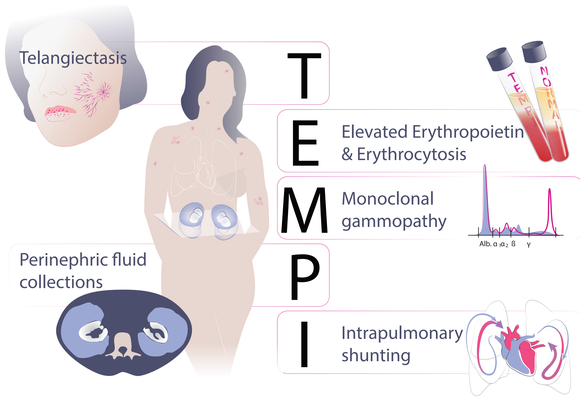
Universiteit Antwerpen

Unique patient specific monoclonal antibodies as tools for target antigen discovery

David B. Sykes [1], Jens Wrammert [2], Wilfried Schroyens [3]

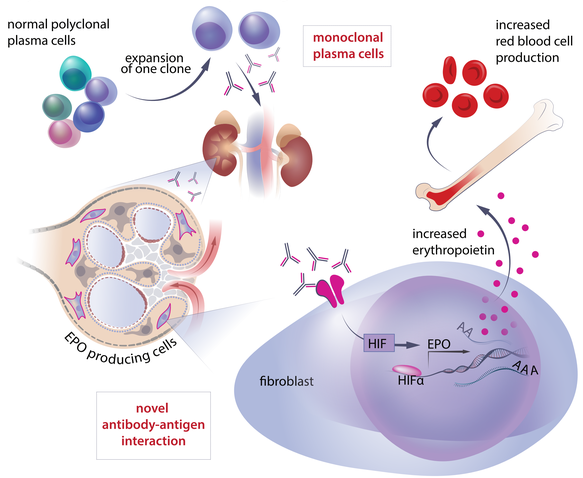
THE TEMPI SYNDROME: A RARE MGCS

- TEMPI: 5 Hallmark disease features
- TEMPI was first described in 2011 (Sykes et al, *NEJM*)
- Reviewed in 2020 (*Blood Spotlight* article)
- The disease affects ~53 known patients worldwide
- It is an acquired disorder affecting patients ~25-75 years old
- Males and females appear equally affected
- No geographic or genetic predisposition



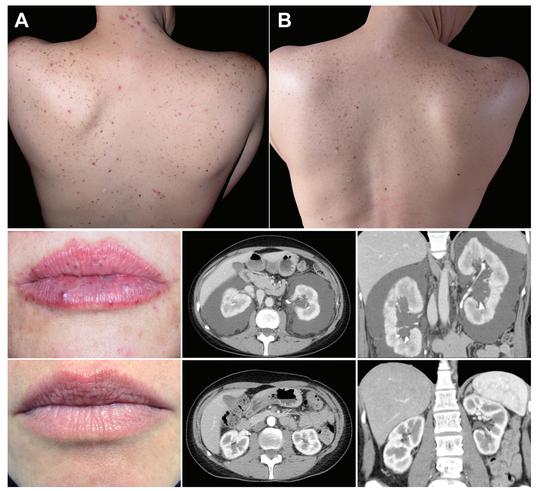
TEMPI MGUS DRIVING EPO PRODUCTION?

- Patients present with marked erythrocytosis
- Commonly misdiagnosed with polycythemia vera
- Elevated serum EPO can exceed 500x the upper limit of normal
- Suggests dysregulation of the hypoxia sensing pathway
- Hypothesis: MGUS is the pathogenic driver of EPO production



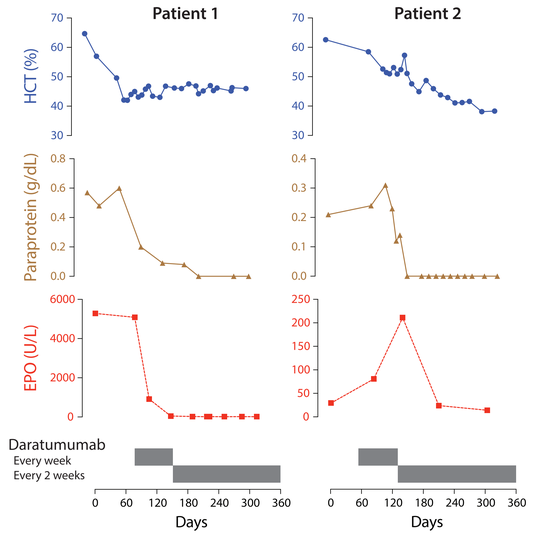
ERADICATING THE MGUS - BORTEZOMIB

- Treatment that eradicates the MGUS reverses the other sequelae of the TEMPI syndrome.
- One patient received single agent bortezomib (*NEJM*, 2012)



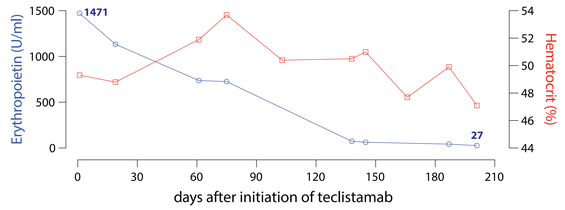
ERADICATING THE MGUS - DARATUMUMAB

- Two patients with TEMPI syndrome relapsed after a long clinical remission following treatment with bortezomib
- Both patients responded dramatically to treatment with single agent daratumumab (*NEJM*, 2018)



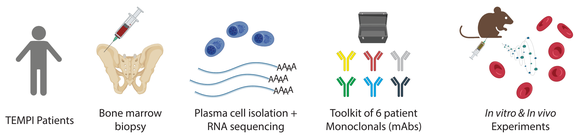
ERADICATING THE MGUS - TECLISTAMAB

- One patient with TEMPI syndrome relapsed after treatment with bortezomib and then treatment with daratumumab. The patient responded dramatically to teclistamab (*NEJM*, 2024)



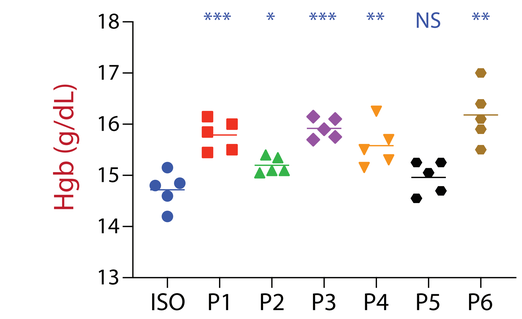
A TOOLKIT OF UNIQUE TEMPI PATIENT mAbs

- Plasma cells (CD38+, CD138+) were isolated from bone marrow aspirates of patients with TEMPI syndrome
- Long read sequencing identified the exact heavy and light chain antibody sequences
- Recombinant monoclonal antibodies (mAbs) were produced in vitro (293T) from patients with TEMPI syndrome
- After more than a decade of research, these now provide a powerful tool for understanding disease pathogenesis
- We now have 11 unique TEMPI patient mAbs



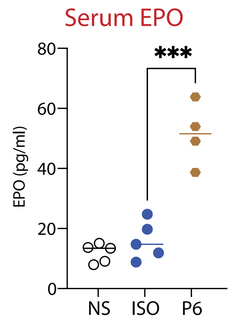
TEMPI mAbs DRIVE ERYTHROCYTOSIS IN MICE

- A single intravenous injection of TEMPI patient mAbs (6 patients) into wild-type recipient mice results in an increase in Hemoglobin (and Hematocrit) at day 7. ISO = Isotype control



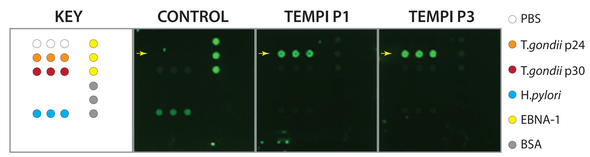
TEMPI mAbs DRIVE EPO PRODUCTION IN MICE

- A single intravenous (retro-orbital) injection of TEMPI patient #6 mAb into wild-type recipient mice
- Results in increased serum Erythropoietin (EPO) at 4 hours (ELISA)
- Normal Saline control, NS, or Isotype control, ISO
- This experiment confirmed the pathogenic nature of the TEMPI patient mAbs driving EPO production



TEMPI mAbs: PATHOGEN MOLECULAR MIMICRY

- A subset (2/6) of the TEMPI patient mAbs show specific binding to Toxoplasma gondii p24 protein
- This suggests that the MGUS may arise in response to an infectious trigger and there there may be some degree of molecular mimicry between the epitope on the pathogen and the auto-epitope driving EPO production



TEMPI mAbs: TARGET IDENTIFICATION

- Our research now focuses on target identification using the **Membrane Proteome Array** platform from *Integral Molecular*.
- Do you have a patient with **TEMPI syndrome** or another interesting MGCS (monoclonal gammopathy of clinical significance)?
  - ---> PLEASE REACH OUT
- A sincere thank you to the **American Society of Hematology** for years of support

Hematopia

Scan the QR code for more information
Please reach out: **dbsykes@mgh.harvard.edu**