Back to the future in MPN

Claire Harrison
Guy’s and St Thomas’ Hospital NHS Foundation Trust, London, UK
Primary Myelofibrosis

1879: Gustav Heuck (1854-1940)

- 2 cases of leukemia with peculiar blood and marrow findings
  - Massive splenomegaly
  - Constitutional symptoms
  - Fibrous material in the bones
• **Louis Henri Vaquez** (27 August 1860 – 1936) was a French Physician

• In 1892 he was the first to describe **polycythaemia vera** or **polycythaemia rubra vera**, which is also known as "Osler-Vaquez disease"

• Vaquez described the disease in a 40-year-old male suffering from chronic cyanosis, distended veins, vertigo, dysnea, hepatosplenomegaly, palpitations and marked erythrocytosis
Hemorrhagic Thrombocytthemia: A Critical Review

By F. W. Gunz

HEMORRHAGIC thrombocytthemia is a term first suggested by Epstein and Goedel\textsuperscript{17} in 1934 as a suitable name for a disorder characterized by repeated hemorrhages, chiefly from the skin and nose, caused by a remarkable increase in the number of platelets. Cases of this nature appear in the literature under the terms of thrombocytosis, essential, hemorrhagia, metaplasia of the bone, and exophytic leukemia, and are differentiated from those of granulocytic leukemia, myelocytic leukemia, and metaplasia of the bone. In all these conditions there is a high count of the platelets. Later known as ESSENTIAL THROMBOCYTHAEMIA or ET
Myeloproliferative milestones

1951 - William Dameshek “Some speculations on the myeloproliferative syndromes”

1974 - Axelrad & Prchal “EPO independence”

1976 - Fialkow - “Stem cell origin”

1980s - PVSG studies reported
“Bloodletting”
18th Century Persian manuscript illustration
1951 - William Dameshek “Some speculations on the myeloproliferative syndromes”

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1980s - PVSG studies reported

2005 - Description of JAK2V617F mutation, ECLAP study and PT-1

2007 - JAK inhibitors reach the clinic

2008 - Phase I/II trials of ruxolitinib reported and PT-1 largest randomised study in ET

2010 - Phase III trials of ruxolitinib reported and FDA approval

2013 - Description of Calreticulin gene mutations

2014 - Phase III trials of ruxolitinib in PV
**Myeloproliferative milestones**

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Beyond \textit{JAK2 V617F} Mutation: Molecular Complexity of MPNs

- **Mutations affecting the JAK-STAT Signaling**
  - \textit{JAK2}
  - \textit{MPL}
  - \textit{LNK}
  - \textit{c-CBL}
  - \textit{SOCS1-3}
  - \textit{CALR}

- **Mutations affecting the epigenetic regulation**
  - \textit{TET2}
  - \textit{EZH2}
  - \textit{ASXL1}
  - \textit{IDH1/2}
  - \textit{DNMT3A}
  - \textit{JAK2V617F}

- **Mutations associated with Leukemic transformation**
  - \textit{IDH1/2}
  - \textit{IKZF1}
  - \textit{TP53}
  - \textit{NF1}
  - \textit{RUNX1}
  - \textit{NRAS}
  - \textit{KRAS}
  - \textit{DNMT3A}
**Order matters**

JAK2-first patients present at a younger age

.... are more likely to present as PV

.... and have increased risk of thrombosis (art + venous)

*Ortmann, Kent et al*  
*NEJM 2015*
First demonstration in any cancer that mutation order influences stem/progenitor cell behaviour, clinical presentation and response to therapy.

Ortmann, Kent et al NEJM 2015
Myeloproliferative milestones

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2008 MPD becomes MPN

MPD support is born later becomes MPN voice

2005 Description of JAK2V617F mutation, ECLAP study and PT-1
Alone we can do so little; together we can do so much.
What’s new and clinical trials?
It's not all about drugs..

Sometimes research is asking a simple question

"how are your symptoms?"

or even just for a small amount of blood this study led to our discoveries of JAK2 and CALR mutations

“Bloodletting”
18th Century Persian manuscript illustration
# MPN trial portfolio in the UK

## ET
- PT-1 low and intermediate risk data collection

## ET and PV
- First line: PEGASYS vs HC MPD RC 112

## Refractory/intolerant to HU: MAJIC
- Response, Relief, ARD12042 - closed

## MF
- ERNEST registry
  - Momelolinib vs Ruxolitinib

### Second line:
- Momelotinib vs BAT anaemic on ruxolitinib
- Pfixer Smo vs BAT
- PERSIST 2 pacritininib vs BAT plts < 100
- Phase I low platelets ruxolitinib
- Telomerase

### Combinations:
- Ruxolitinib+Pbinostat,+BKM120,+LDE225
- Ruxolitinib pre BMT study MPD RC114

## MDS/AML after MPN:
- Phazar - data collection only / ruxolitinib + 5 azacytidine

### All MPN: MEASURES for symptoms
- MOSAICC epidemiology
- Sample banks - Nick Cross and Tony
WHY DO MPNs DEVELOP??

CIs: Mary Frances McMullin, Andrew Duncombe, Lesley Ashton
A RandoMised study of best Available therapy versus JAK Inhibition in patients with high risk Polycythaemia Vera or Essential Thrombocythaemia who are resistant or intolerant to HydroxyCarbamide

Only on-going study in PV ( & ET) likely to answer questions about transformation and thrombosis

40 slots left for PV patients
# JAK1 & 2 Inhibitors in MPNs – Efficacy Summary

<table>
<thead>
<tr>
<th></th>
<th>Myelofibrosis</th>
<th>Polycythemia Vera</th>
<th>Essential Thrombocythemia</th>
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</thead>
<tbody>
<tr>
<td>SAR302503 – PH III JAKARTA (HOLD)</td>
<td>P III</td>
<td>P III</td>
<td>P II</td>
</tr>
<tr>
<td>Pacritinib- PIII Ongoing (Persist 1 complete MF)</td>
<td>P II</td>
<td>P II</td>
<td>P II</td>
</tr>
<tr>
<td>CYT387 – Momelotinib SIMPLIFY studies</td>
<td>P II</td>
<td>P II</td>
<td>P II</td>
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<tr>
<td>LY2784544</td>
<td>P I</td>
<td>P I</td>
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<td>NS-018</td>
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<tr>
<td>BMS-911543</td>
<td>PH II</td>
<td>PH II</td>
<td></td>
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<tr>
<td>INCB039110 (JAK1 Alone)</td>
<td>P I</td>
<td>P I</td>
<td>P I</td>
</tr>
<tr>
<td>CEP701</td>
<td>P II</td>
<td>P II</td>
<td>P II</td>
</tr>
</tbody>
</table>

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Not Reported Yet

Occasional

Ongoing Trials

No
## Pacritinib

**A Selective JAK2/FLT3 Inhibitor**

- Not associated with clinically significant treatment-emergent anemia or thrombocytopenia in clinical studies\(^1\)

### Kinase IC\(_{50}\) (nM)

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC(_{50}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK1</td>
<td>no effect at 100 nm</td>
</tr>
<tr>
<td>JAK2(^{wt})</td>
<td>6.0</td>
</tr>
<tr>
<td>JAK2(^{V617F})</td>
<td>9.4</td>
</tr>
<tr>
<td>JAK3</td>
<td>18.3</td>
</tr>
<tr>
<td>TYK2</td>
<td>27.0</td>
</tr>
<tr>
<td>FLT3-ITD</td>
<td>13.4</td>
</tr>
<tr>
<td>FLT3(^{D835Y})</td>
<td>4.7</td>
</tr>
<tr>
<td>CSF1R</td>
<td>39.5</td>
</tr>
<tr>
<td>IRAK1</td>
<td>13.6</td>
</tr>
</tbody>
</table>

CSF1R, colony stimulating factor 1 receptor; FLT, FMS-like tyrosine kinase; IC\(_{50}\), half-maximal inhibitory concentration; IRAK1, interleukin-1 receptor–associated kinase; ITD, internal tandem duplication; JAK, Janus kinase; TYK, tyrosine kinase.

Phase 3 Trials with Pacritinib

**Enrollment Complete:** N = 327; Topline data Q1 2015

**Sites:** ~90 in Europe, Australia, Russia and U.S.

**Principal Investigators:** Ruben Mesa, M.D., Mayo Clinic Cancer Center, Arizona
Claire Harrison, M.D., Guy’s Hospital, London

*Cross-over from BAT allowed after progression or assessment of the primary endpoint.*
RESULTS OF PERSIST-1 TRIAL

Spleen Volume Reduction $\geq 35\%$ *At Week 24 as Assessed by MRI/CT*

- **ITT population**: 19.1\% vs 4.7\%, PAC vs BAT ($p=0.0003$)
- **Evaluable* population**: 25.0\% vs 5.9\%, PAC vs BAT ($p=0.0001$)

\[\text{Change From Baseline, } \%\]

Patients

$^a$ Patients had both baseline and Week 24 spleen assessment by MRI or CT.

BAT, best available therapy; CT, computed tomography; ITT, intent to treat; MRI, magnetic resonance imaging; PAC, pacritinib.
Less “Myelosuppression” With Pacritinib: Platelets and Hemoglobin Over Time……..

**Mean Platelets $\times 10^9$/L ($\pm$ SEM)**

- **Patients With Baseline Platelets <50,000/μL**
  - $p=0.0034^a$

**Mean Hgb (g/dL) ($\pm$ SEM)**

- **Patients With Baseline Hgb <10 g/dL**
  - $p=0.1927^a$

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$a$ Based on linear regression using mixed model.

BAT, best available therapy; PAC, pacritinib; SEM, standard error of the mean.
**Status:** Reached agreement with FDA on SPA in Oct. 2013; First patient randomized August 2014

**Sites:** Predominantly U.S.; Europe, Australia, New Zealand and Russia

**Principal Investigator:** Srdan Verstovsek, M.D., MD Anderson, Texas

**Anticipated Patient Accrual:** ~10-12 months (target LPFV Q1 2015)

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1 Cross-over from BAT allowed after progression or assessment of the primary endpoint

2 BAT may include ruxolitinib at the approved dose for platelet count
Momelotinib (CYT387)

• Momelotinib is an oral small-molecule, ATP-competitive, JAK1 and JAK2 inhibitor

• A previous phase I/II study of momelotinib in subjects with myelofibrosis (n = 166) demonstrated improvements in splenomegaly, symptoms and anaemia\(^1\)

\(^1\)Pardanani et al. ASH 2012
Phase 3 Studies with Momelotinib 200 mg Tablet QD for Myelofibrosis

**SIMPLIFY-1**
*JAK inhibitor naïve*
- Randomized, Double Blind
- Primary endpoint: Spleen Response by MRI at week 24

**SIMPLIFY-2**
*Previous JAK inhibitor exposure*
- Randomized, Open Label
- Required ruxolitinib dose adjustment to < 20mg BID and concurrent hematologic toxicity
- Primary endpoint: Spleen Response by MRI at week 24
Therapies being tested WITH JAK2 inhibitors

- Allogeneic Hematopoietic Cell Transplantation
- Danazol (androgenic steroids)
- IMiD (lenalidomide or pomalidomide)
- Erythropoietin-stimulating agents
- GS-6624 (LOXL2)
- Azacytidine
- Decitabine
- Panobinostat
- BKM120
- Hh inhibitors (LDE125)

**WHY:**

Get a BETTER RESPONSE and/or
Reduce toxicity (anaemia)

**Planned:**

- RAD001 (Everolimus)
- MEK inhibitor
- PRM-151
- Pfizer Smo inhibitor

**BUT who should these strategies be tested in and what should the endpoints be??**
### “Newer” Drugs for MPN (Excluding JAKi)

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent*</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3K pathway inhibitors</td>
<td>• BKM120/Buparlisib&lt;br&gt;• RAD001/Everolimus</td>
<td>PI3K/Akt/mTOR</td>
</tr>
<tr>
<td>Histone deacetylase (HDAC) inhibitors</td>
<td>• Panobinostat&lt;br&gt;• Vorinostat&lt;br&gt;• Givinostat&lt;br&gt;• Pacrinostat</td>
<td>HDACs (different classes)&lt;br&gt;HSP90</td>
</tr>
<tr>
<td>DNA methyltransferase inhibitors</td>
<td>• Azacitidine&lt;br&gt;• Decitabine</td>
<td>DNA methyltransferase</td>
</tr>
<tr>
<td>Hedgehog inhibitors</td>
<td>• LDE225</td>
<td>Smo</td>
</tr>
<tr>
<td>Telomerase inhibitors</td>
<td>• Imetelstat</td>
<td>Telomerase</td>
</tr>
<tr>
<td>Bone marrow fibrosis inhibitors</td>
<td>• Pentraxin</td>
<td>DAMPs and monocytes / macrophages</td>
</tr>
</tbody>
</table>

* list not exhaustive
A Pilot Study of the Telomerase Inhibitor Imetelstat for Myelofibrosis

Ayalew Tefferi, M.D., Terra L. Lasho, Ph.D., Kebede H. Begna, M.D., Mrinal M. Patnaik, M.D., Darci L. Zblewski, C.N.P., Christy M. Finke, B.Sc., Rebecca R. Laborde, Ph.D., Emnet Wassie, M.D., Lauren Schimek, B.S., Curtis A. Hanson, M.D., Naseema Gangat, M.D., Xiaolin Wang, Ph.D., and Animesh Pardanani, M.D., Ph.D.
Some patients achieve remission!
Where we’re going, we don’t need roads.
World first use of gene-edited immune cells to treat ‘incurable’ leukaemia

05 November 2015

A new treatment that uses ‘molecular scissors’ to edit genes and create designer immune cells programmed to hunt out and kill drug resistant leukaemia has been used at Great Ormond Street Hospital (GOSH).

The treatment, previously only tested in the laboratory, was used in one-year-old, Layla, who had relapsed acute lymphoblastic leukaemia (ALL). She is now cancer free and doing well.

This breakthrough comes from GOSH and UCL Institute of Child Health’s (ICH) pioneering research teams, who together are developing treatments and cures for some of the rarest childhood diseases.

Chemotherapy successfully treats many patients with leukaemia but it can be ineffective in patients with particularly aggressive forms of the disease where cancer cells can remain hidden or resistant to drug therapy. Recent developments have led to treatments where immune cells, known as T-cells, are gathered from patients and programmed using gene therapy to recognise and kill cancerous cells. Multiple clinical trials are underway, but individuals with leukaemia, or those who have had several rounds of chemotherapy, often don’t have enough healthy T-cells to collect and modify meaning this type of treatment is not appropriate.

A team at GOSH has now used modified T-cells from donors, known as UCART19 cells, to treat a one-year-old child with an aggressive form of ALL who had unsuccessful chemotherapy and for whom palliative care was deemed the only option left.

The treatment works by adding new genes to healthy donor T-cells, which arm them against leukaemia. Using molecular tools (TALEN®) that act like very accurate scissors, specific genes are then cut in order to make the T-cells behave in two specific ways. Firstly, the cells became invisible to a powerful leukaemia drug that would usually kill them and secondly they are reprogrammed to only target and fight against leukaemia cells.

The team at GOSH and the UCL ICH, along with investigators at University College London and biotech company Cellectis, had been developing ‘off-the-shelf’ banks of these donor T-cells and the first of which was due to be used for final stage testing ahead of clinical trials. But after hearing about this infant, the team received special permission to try the new treatment early.

Professor Wassem Qasim, Professor of Cell and Gene Therapy at UCL ICH and Consultant Immunologist at GOSH, explains: “The approach is not without risk, but it has the potential to be a real breakthrough…”
CRISPR: Gene Therapy Finally Coming to MPNs?

Clustered Regularly Interspaced Short Palindromic Repeat

Bacterial immune response system leveraged for genome editing
The landscape is changing

Thanks to many patients, teams & colleagues for dedication & sharing data