Lymphoma Therapeutics and Diagnosis Research: Needs and Trends

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Lymphoma Incidence and Prevalence

In France in 2010, 5\textsuperscript{th} most frequent cancer, 8\textsuperscript{th} in terms of mortality related to cancer\textsuperscript{1}

Estimated 16,854 new cases in 2012 in France\textsuperscript{2}, about 70,000 in the US (excluding CLL and PCD)\textsuperscript{3}

From 1997 to 2000, incidence steadily increased (~3.5%/year) but appears now stable or slightly decreasing\textsuperscript{2}

\textsuperscript{1} INCA statistics, 2012; 2013 . 2. Le Guyader-Perou, Rev Fran Epidem et Sante Publique, 2016. 3. Terras et al. CA Cancer J Clin 2016
Multiple Different Diseases

About 80 different entities based upon clinical morphological, immunological, cytogenetic and molecular features

- ~ 50 B-cell lymphoma subtypes; 28 T-cell lymphoma subtypes
- plus Hodgkin and post-transplant lymphomas

High level of expertise needed
About 115,000 patients die each year in Europe from blood diseases.

The combined societal cost of hematologic diseases for the EU, Norway, Iceland, and Switzerland has been estimated at €22.5 billion per year.

At the European level, public spending on hematology research currently does not match this vast medical need.

- Of the €6.1 billion that the European Union allocated to health research under its 7th Framework Program (2007 to 2013), only 2.2% (€137 million) was granted to hematology research. That amounts to less than 0.1% of the societal cost of blood disorders in Europe over that same period.
The European Hematology Association
Roadmap for European Hematology Research: a consensus document

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To the editor:

A roadmap for discovery and translation in lymphoma

Further achievements in understanding the biology of lymphoid malignancies will be made possible only if major investments can be realized in
- Tumor genomic (NGS, functional assays)
- Microenvironment +++
- And also host genetics

These efforts should particularly focus on establishing new cellular and animal models (critically rare in the field of mature lymphoid malignancies) to better understand how these diseases develop and to preclinically assess new therapeutic agents.
On the clinical side, specific goals include

- Increasing cure rate
  - critical in T-cell and some aggressive B-cell
  - an open challenge for indolent lymphomas

- Avoiding short and long term toxicities
  - Immediate treatment related as well as
    long term side effects (CV toxicities, infections, fatigue, …)

- Paying more attention to extreme ages
Reinforce the ability of cooperative group to perform academic studies and extend the field to socio-economic issues.

Further support their translational research activities, especially their efforts to constitute and analyze large biobanks with high-quality clinical annotations.
Lymphoma Diagnosis (I)

A multidisciplinary approach

- Clinical presentation
- Morphology
- Immunology
- Molecular cytogenetics
- Mutations, CNV, etc…
A multidisciplinary approach

- Clinical presentation: PET-CT
- Morphology: new microscopy tools
- Immunology: CMF, CyTOF, CAI
- Molecular cytogenetics
- Mutations, GEP, CNV, etc
Several challenges for modern diagnosis

- Multiple complementary tools
  - Constantly evolving techniques
  - Costs
- Need for replication and cross-validation
  - Large annotated sample collections with quality clinical data
- Integration of all data, bioinformatics
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Other emerging challenges

- Blood vs. tissue derived biomarkers
- Immunomonitoring
- Minimal residual disease
- Theranostic markers (IO biomarkers)
Immune interventions in development

- Antibodies targeting tumor antigens
  - Naked, immuno-conjugates, radiolabelled
  - Bi-specifics

- Antibodies targeting microenvironment
  - Immune checkpoint blockers, NK targets, etc…

- Immunomodulatory agents
  - IMIDs, etc…

- CAR-T cells
Targeted therapies in clinical development today:

- **BCR signalling**
  - BTK inhibitors, PI3K inhibitors, SYK, mTOR, etc...

- **Apoptosis**
  - BCL2 inhibitors, MCL1, …

- **Epigenetics**
  - HDAC, EZH2i, BETi

- **Intracellular trafficking**
  - XPO1 inhibitor

- **Metabolism**
  - IDH1 & 2 inhibitor
Agents potentially active in “all” B-cell lymphoma
- Compounds active on “the immune response”
- Compounds increasing anti-CD20 activity
- Other B-cell antigens: naked Ab or ADC
- B-cell antigens: radio-immunotherapy
- Bispecific Abs...

Agents active on specific entities
- Molecularly defined subsets
- Pathways (signaling, apoptosis)
- Various (epigenetics modifiers? others?)
Single agents versus combinations?
- Unique oncogenic pathway in lymphoma?
- With commonly used regimens?
- With other new agents?
- Rationale design?
- Issues of toxicities…

What is the treatment goal?
- Cure or palliation…
- Depends on lymphoma entities and line of treatment…
Many studies, many patients: merging efforts
- Molecular selection
- Translational studies ++

Biases of patient selection in phase I studies

Complexity of designing trials in “small” populations

How to move from early to final data (and drug approval)?
- Skipping phase II OR large convincing phase II?
- New trial designs?
In Conclusion

Many unmet medical needs in the lymphoma field

Industry and academia should partner to address them

CALYM is an academic partner to many life science companies for the acceleration of innovation and its transfer in the lymphoma field
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→ TOGETHER we can advance lymphoma diagnosis and treatment