The Impact of Biological Ageing on Development and Therapy of Breast Cancer

Dr. Barbara Brouwers
Prof. Dr. Hans Wildiers – Prof. Dr. Diether Lambrechts
Dr. Sigrid Hatse
The Biology of Ageing

- Genetics
- Environmental Factors
- Diseases/Comorbidities
- ...

www.123rf.com
Cellular Senescence
Ageing protects against Cancer

Finkel et al, Nature 2007; 448
Shan et al, 2009. Frontiers in Bioscience, 1;14 : 4044-57
Ageing protects against Cancer

Cellular Senescence
Ageing causes Cancer

Tumor growth stimulated by fibroblasts.

Krtolica A et al. PNAS 2001;98:12072-12077

©2001 by National Academy of Sciences
Epithelial tumors stimulated by senescent human fibroblasts progress to full malignancy.
Diagram representing the different positions of the theories of aging on the prevention versus enhancement of aging and cancer.

Falandry C et al. JCO 2014;32:2604-2610
Research Questions

**Hypothesis 1**
Biological ageing in the host creates a growth-en-metastasis stimulating microenvironment

**Hypothesis 2**
Chemotherapy accelerates biological ageing in the host

- Geriatric Assessment
- Biomarkers of Ageing

Stromal Gene Expression Study

B-CGA-1 study
Elderly Biomarker Study
Elderly Stromal Gene Expression Study
Materials and Methods

(in cooperation with I. Bordet – D. Fumagalli / C. Sotiriou)

Tumors are matched for:
- Tumor Grade
- Tumor Size
- Nodal Status

Laser Capture Microdissection of tumor associated stroma

- RNA extraction
- RNA amplification
- Microarray Gene expression Analysis on RNA

10 OLD PATIENTS (> 80 y)
10 YOUNG PATIENTS (< 45 y)
RESULTS

Angiogenesis

Matrix Remodelling
RESULTS cytokines
RESULTS autophagy/senescence transition

autophagy

pval = 0.273

glycolysis

pval = 0.121
2. Chemotherapy → ↑Biol Ageing?

How to measure biological age?

1. Clinical Measures
   - Calendar Age?
   - CGA items
   - Classification of Balducci
     - FIT
     - VULNERABLE
     - FRAIL
   - Better way of using the information of geriatric assessment?

2. Biomarkers of Ageing
   - Telomere length in WBC
   - Cytokines/Chemokines circulating in the blood
   - Endocrine markers/Growth Factors (eg. IGF-1)
   - Phenotype profile of circulating WBC subsets
2 projects to answer these questions

• Value of **different clinical and biological markers** in reflecting biological age and the relationship between each other
  → **B-CGA-1 study** (retrospective)

• Use of these different markers in studying the **effect of chemotherapy** on the ageing process
  → **EBS** (prospective)
2.1 B-CGA-1 Study
RETROSPECTIVE

BIOMARKERS + COMPREHENSIVE GERIATRIC ASSESSMENT IN THE OLDER GROUP

N = 160

N = 80

Brouwers B et al, manuscript in preparation for submission to Clinical Cancer Research
Biomarkers ~ Calendar Age

**Telomeres (T/S ratio)**

**IL-6**

**IGF-1**

**MCP1**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>N</th>
<th>Spearman</th>
<th>P</th>
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<tbody>
<tr>
<td>Telomere Length</td>
<td>196</td>
<td>-0.396</td>
<td>&lt;.0001</td>
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<tr>
<td>IL-6</td>
<td>238</td>
<td>0.272</td>
<td>&lt;.0001</td>
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<tr>
<td>IGF-1</td>
<td>213</td>
<td>-0.529*</td>
<td>&lt;.0001</td>
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<td>MCP-1</td>
<td>238</td>
<td>0.412</td>
<td>&lt;.0001</td>
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<td>RANTES</td>
<td>238</td>
<td>-0.106</td>
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### Biomarkers ~ Frailty/Clinical Ageing

#### SUBSCORES IN GERIATRIC ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>IGF-1</th>
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<th></th>
<th>IL-6</th>
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<td>141</td>
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<td>MMSE</td>
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<td>152</td>
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<td>GDS_15</td>
<td>130</td>
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<td>152</td>
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<td>65</td>
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<tr>
<td>Charlson</td>
<td>133</td>
<td>-0.195</td>
<td>0.0248</td>
<td>158</td>
<td>0.154</td>
<td>0.0539</td>
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</tbody>
</table>

#### BALDUCCI

**IL-6**
- N= 158
- Fit : 1.4 - Vulnerable : 2.3 - Frail : 2.8 (pg/ml)
- p-value = 0.019

#### Leuven Oncogeriatric Frailty Score (LOFS)
- **IL-6**
  - N= 129
  - Spearman coeff -0.218
  - p-value = 0.0131
Conclusions of B-CGA-1 study

• **IL-6** most strongly correlated with frailty status

• **Other markers** not clearly correlated with frailty, but do significantly change with calendar age

• → do in some way still reflect part of the ageing process

• **LOFS** could be an optimal way of summarizing CGA data for an individual patient
2.2 Elderly Biomarker Study

CHEMOTHERAPY
N = 62
4 * Docetaxel - Cyclophosphamide

CONTROL
N = 57
Aromatase Inhibitor

BIOMARKERS AGEING
• Telomere Length
• IL-6, IL-10, TNF-α
• RANTES, MCP-1
• IGF-1
• (p16)
• Subsets of circulating WBC (immunageing)

POPULATION
≥ 70 years
Operated for Early Breast cancer
Assigned adjuvant chemotherapy or hormonal therapy

GERIATRIC ASSESSMENT
• G8 (geriatric screening test)
• ADL/iADL
({instrumental}Activities of Daily Life)
• Fear of Falls Questionnaire
• EORTC QoL
• MMSE-30
• MNA-SF (Mini Nutritional Assessment, SHORT FORM)
• Charlson Co-morbidity Index

Brouwers et al, in preparation for submission to J. Clin Oncol
Primary Endpoint: Telomere Evolution

NO DIFFERENCE IN EVOLUTION
TEST FOR INTERACTION $p = 0.88$
Other Biomarkers

- **RANTES**
  - Control: Decrease over time
  - Chemo: Steady decrease
  - Statistical significance: p < 0.0001

- **IL-6**
  - Control: Increase over time
  - Chemo: No significant change
  - Statistical significance: p = 0.01

- **MCP-1**
  - Control: Decrease over time
  - Chemo: Steady decrease
  - Statistical significance: p < 0.0001

- **IGF-1**
  - Control: Steady increase over time
  - Chemo: Steady increase over time
  - Statistical significance: p = 0.006, p < 0.0001

- **TNF-α**
  - Control: Steady increase over time
  - Chemo: Steady increase over time
  - Statistical significance: p = 0.001, p < 0.0001

- **IL-10**
  - Control: Steady decrease over time
  - Chemo: Steady decrease over time
  - Statistical significance: P = 0.04, P < 0.0001
Evolution Clinical Parameters

LOFS
Leuven Oncology Frailty Score

Global Health Status

\[ p = 0.0007 \]
Correlations

- **IL-6** and **TNF-α** correlated most strongly with chronological age.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Spearman correlation</th>
<th>P-value</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>T/S</td>
<td>-0.109</td>
<td>0.3198</td>
<td>86</td>
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<tr>
<td>IL-6</td>
<td>0.318</td>
<td>0.0008</td>
<td>108</td>
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<tr>
<td>IL-10</td>
<td>-0.028</td>
<td>0.7796</td>
<td>101</td>
</tr>
<tr>
<td>IGF-1</td>
<td>-0.096</td>
<td>0.3298</td>
<td>106</td>
</tr>
<tr>
<td>TNF-a</td>
<td>0.342</td>
<td>0.0003</td>
<td>108</td>
</tr>
<tr>
<td>MCP-1/CCL-2</td>
<td>0.179</td>
<td>0.0652</td>
<td>107</td>
</tr>
<tr>
<td>RANTES/CCL-5</td>
<td>-0.014</td>
<td>0.8836</td>
<td>107</td>
</tr>
</tbody>
</table>

- **IL-6** correlated most strongly with **LOFS** (spearman -0.209, p=0.0313).

- In Chemo cohort, **MCP-1** and **RANTES** were associated with **functional** decline (iADL ≥1 point decline at 1y).

- No biomarkers were associated with QoL decline and grade II-III-IV toxicity.
Conclusion

- **Breast cancer micro-environment** in older patients:
  - Higher angiogenesis
  - More Matrix Remodeling
  - More pro-inflammatory cytokines
  - More autophagy/senescence transition could not be confirmed

- **IL-6** most strongly correlates with **frailty status**
- Other markers do not clearly correlate with frailty, but do significantly change with **calendar age**

- **Biomarker evolution during chemotherapy** did not differ significantly when compared with a control group at a timepoint of 1 year after start of adjuvant treatment
- Neither was there a difference in evolution of **geriatric assessment results**
Many Thanks to ...

• All patients participating in the study and all patients consenting for the MBC blood bank
• Prof. Dr. Hans Wildiers, Prof. Dr. Diether Lambrechts
• Dr. S Hatse – Bruna S. Dalmasso – K Corthouts
• Cindy Kenis – Sanne De Coster – Britt Leys
• Dr. D. Fumagalli, Prof. Dr. C. Sotiriou, S. Brohée
• Pathology Department of UZ Leuven – Prof. Dr. G. Floris

• All other members of LEO & ExpRT as well as physicians, nurses (and others) of the hospital supporting and helping with the Elderly Biomarker Study
• Research Funds: Vlaamse Liga tegen Kanker, Stichting tegen Kanker, Fonds voor Wetenschappelijk Onderzoek Vlaanderen
Oncology, fellowship and networking

Evandro de Azambuja, MD, PhD
Department of Medicine, BrEAST Data Centre
Institut Jules Bordet
Brussels, BE
About me...

• Medical oncologist fully trained in Porto Alegre, Brazil
• Specialization in Internal Medicine and Medical Oncology
• Master degree in Medical Sciences
• PhD in Medical Sciences
A few months later...
My first take home message...

Identify a good mentor

And do not be afraid of making contacts
But why was I looking for a change?

• To acquire skills in clinical research
• To acquire skills in developing and running international clinical trials
• To have an international experience in clinical work
• To open my mind to new techniques, drugs, etc...
What did I learn between 2003-2015?

• Networking

• Research cannot stand alone: there is a need for collaboration

• You have to work hard if you want to achieve your goals

• Pass on your knowledge: do not be afraid of sharing/discussing information, ideas, etc...

• Dedicate some time to think
How ESMO played a role in this?
ESMO: 2005-2015

• Member since 2005
• Member of the ESMO Young Oncologist Committee 2009-2013
• Member of the ESMO Press Release Committee since July 2011
ESMO: 2005-2015

• Co-chair of the **Young Oncologist Track for ECCO-ESMO** conference 2013 (Amsterdam)

• Chair of the **Early Breast Cancer track ESMO** conference 2014 (Madrid)

• **Editor-in-chief for the Daily News at the ESMO Conference** 2014 (Madrid)
Young Oncologists: the leaders for tomorrow

37% of ESMO active members are younger than 40 years old

Source: ESMO Membership statistics December 2014
My second take home message...

To invest time in committees and societies

Be committed, reliable and share your vision
What were the other opportunities I had?
Benefiting from opportunities

• Innovators in breast cancer (NYC)

• Innovators in breast cancer UK
  – Mentorship
  – Collaboration
  – Leadership

• European Science Communication Network (ESConet)
ASCO Experience

2014 Oncology Literature Reviews

Updates in Breast Cancer

Third Quarter

Evandro de Azambuja, MD, PhD
Jules Bordet Inst
Brussels, Belgium

Planning Group
Aditya Bardia, MD
Massachusetts General Hospital Cancer Institute
Cambridge, MA

ASC0 University
My third take home message...

To interact with knowledgeable people

They are people like you!
Why can research not stand alone?
What is BIG?

- **International** non-profit organisation
- **Network of academic** breast cancer research **groups / data centres**
- Founded in **1999** by European opinion leaders in breast cancer
- **55** members tied to **several thousand hospitals** worldwide
- **>30 clinical trials** ongoing or under development
- **Member group data centres** manage trials
- **Brussels-based headquarters** provides support services

Courtesy of BIG
What is BIG vision & mission?

We will find a cure for breast cancer through global research and collaboration

Facilitating breast cancer research internationally

10 Key Principles of Research Conduct

1. Advance knowledge ➔ Serve patients
2. Retain independence
3. Database control / statistical leadership
4. Steering Committee
5. Independent Data Monitoring Committee
6. Trial monitoring
7. Presentations / publications – academic standards
8. GCP / regulatory standards
9. Biological specimen collection for future research
10. Long-term follow-up of patients

Courtesy of BIG
Who is in BIG?

55 BIG Members Worldwide

EU: 28 COUNTRIES + Switzerland, Norway, Iceland, Former Rep of Macedonia, Turkey

ISRAEL
EGYPT

INDIA
HONG KONG
PAKISTAN
SINGAPORE
TAIWAN

AUSTRALIA
JAPAN
NEW ZEALAND

ARGENTINA
BRAZIL
CHILE
PERU
URUGUAY
& multiple other Latin American / Caribbean countries

Russia

Nigeria
South Africa

Large multinational trials
e.g. HERA, MINDACT, (Neo)ALTTO, APHINITY

National GROUPS or International GROUPS / centres

Courtesy of BIG
The BIG experience: activating clinical trials and recruiting patients

Single HER2 blockade vs observation

Trastuzumab

HERA

478 sites
39 countries

5102 Pts in 43 months

Europe
3850 (75%)
North America
160 (3%)
South America
284 (6%)
Australasia
808 (16%)

Dual HER2 blockade vs single HER2 blockade

Trastuzumab + Lapatinib

ALTTO

946 sites
44 countries

8381 Pts in 49 months

Europe
4470 (54%)
North America
959 (11%)
South America
444 (5%)
Australasia
2508 (30%)

Trastuzumab + Pertuzumab

APHINITY

563 sites
42 countries

4805 Pts in 21 months

Europe
2721 (57%)
North America
700 (15%)
South America
124 (3%)
Australasia
1259 (26%)

Adapted from M. Piccart
What if ALTTO had a similar accrual as HERA?

- HERA: 43 months, 5,102 patients
- ALTTO: 49 months, 8,381 patients

Simulation:

50% sites and similar # of countries
Based on HERA monthly accrual
42% longer accrual and delay in results!
Fellowship: the best way of networking!

36 fellows, colleagues, collaborators and friends in 15 countries
My fourth take home message...

Collaboration is crucial
Publication opportunities
Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology

1, Thomas Force 2, Michael S. Ewer 3, Gilles W. de Keulenaer 4, Stefan D. Anker 5, Metin Avkiran 6, Evandro de Azambuja 7, Dirk L. Bruaart 8, Gianlugi Condorelli 9, Arne Hansen 10, Joseph A. Hill 11, Emilio Hirsch 12, Denise Hilfiker-Kleiner 13, Sven de Jong 14, Gude Neubauer 15, Burkert Pieske 16, Ilwin Pirmohamed 17, Mathias Rauchhaus 18, Douglas Sawyer 19, Johann Wojta 20, Faiez Zannad 21, and Ajay M. Shah 22

Clinical practice guidelines

The Lancet Oncology Commission

Planning cancer control in Latin America

Luminal B Breast Cancer: Molecular Characterization, Clinical Management, and Future Perspectives

Felipe Ares, Dimitrios Zarandavis, Ivana Bezzovic-Saposjevic, Lina Pagliano, Debora Fumagalli, Evandro de Azambuja, Giuseppe Viale, Christos Sozzi, and Martine J. Piccart
My fifth take home message...

Good quality writing
Acknowledgments (I)
Acknowledgments (II)