What is the current state of breast cancer classification?

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Why subtyping?

Breast cancer is a heterogeneous disease:
- Histological features
- Biological characteristics
- Clinical outcome
- Responsiveness to therapies

Need for classification
Juliet:
"What's in a name? That which we call a rose
By any other name would smell as sweet."

*Romeo and Juliet (II, ii, 1-2)*
The “perfect” classification

- Clinically useful
  - Prognostic/Predictive
- Scientifically accurate
- Applicable
  - Easy to teach, easy to learn
  - Affordable (time and resources)
- Reproducible
Histopathological Classification (WHO, 2012)

- Ductal carcinoma, n.o.s.
- Lobular carcinoma
  - Classic
  - Variants
- Special types
  - Cribriform
  - Tubular
  - Medullary
  - Apocrine
  - Micropapillary
  - Metaplastic
  - Mucinous
  - ..........
Histopathological Classification

- Highest number of types and subtypes
- Two major types include some 80% of the cases
- It has minimal prognostic/predictive value (clinical utility?)
- Some “special” or “variant” subtypes have clinical implications
<table>
<thead>
<tr>
<th><strong>Highly Endocrine responsive</strong></th>
<th><strong>Non endocrine responsive</strong></th>
<th><strong>Incompletely endocrine responsive</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>□ High ER &amp; PgR <strong>and</strong></td>
<td>□ ER &amp; PgR both absent</td>
<td>• Low ER &amp; PgR <strong>or</strong></td>
</tr>
<tr>
<td>□ No HER2 overexpr <strong>and</strong></td>
<td></td>
<td>• PgR absent <strong>or</strong></td>
</tr>
<tr>
<td>□ Low Ki-67</td>
<td></td>
<td>• HER2 overexpr <strong>or</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• High Ki-67</td>
</tr>
</tbody>
</table>
Biological Classification

- Kind of “Working formulation for clinical use”
- Lowest number of subtypes
- Tumours with different prognosis in the same category
- Issues of reproducibility
Unsupervised analysis of global gene expression patterns unveiled distinct and robust molecular subtypes of breast cancer (496 genes)
Molecular Classification

- 4-6 subtypes
- Tumours with different prognosis in the same category (e.g., Basal-like)
- Issues of affordability
BL tumors are heterogeneous

- IDC NOS, high-grade
- ILC high-grade, pleomorphic
- Metaplastic, high-grade
- Myoepithelial carcinoma
- High-grade (oat-cell) neuroendocrine
- Apocrine
- Medullary
- Adenoid-cystic
- Metaplastic, low-grade
  - Low grade adenosquamous
  - Fibromatosis-like

Poor prognosis

Good prognosis
When I want to read a good novel
I write one!

(Benjamin Disraeli, 1804-1881)
<table>
<thead>
<tr>
<th>‘Subtype’</th>
<th>Type of therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surrogate IHC markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Luminal A’</td>
<td>Endocrine therapy alone</td>
<td>Few require cytotoxics (e.g. high nodal status).</td>
</tr>
<tr>
<td>ER and/or PgR positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 negative, Ki-67 low (&lt;14%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Luminal B (HER2 neg)’</td>
<td>Cytotoxics + endocrine therapy</td>
<td>Inclusion and type of cytotoxics may depend on perceived risk and patient preference.</td>
</tr>
<tr>
<td>ER and/or PgR positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 negative, Ki-67 high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Luminal B (HER2 pos)’</td>
<td>Cytotoxics + anti-HER2 + endocrine therapy</td>
<td>No data are available to support the omission of cytotoxics in this group.</td>
</tr>
<tr>
<td>ER and/or PgR positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘HER2 positive (non luminal)’</td>
<td>Cytotoxics + anti-HER2</td>
<td></td>
</tr>
<tr>
<td>‘Triple negative (ductal)’</td>
<td>Cytotoxics</td>
<td>Consider DNA disrupting agents.</td>
</tr>
<tr>
<td>‘Special histological types’*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Endocrine responsive</td>
<td>Endocrine therapy</td>
<td>Medullary and adenoid cystic carcinomas may not require any adjuvant cytotoxics.</td>
</tr>
<tr>
<td>B. Endocrine non responsive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A clinically useful classification for a personalized cancer medicine: premises

- Genetic aberrations exist in human malignancies
- Some of them “drive” oncogenesis and tumour progression
- These genetic aberrations are potentially “druggable”
- There are tolerable and effective medicinal compounds to target these aberrations
Personalized Cancer Medicine: where are we in Breast Cancer?

- Somatic genetic aberrations are responsible for approximately 90% of breast cancers
- Multiple regions of gene copy gain (17q12)
- High-frequency somatic point mutations
  - TP53 (44%); PIK3CA (26%); CDH1 (19%)
- Low-frequency recurrent point mutations in druggable target genes (KRAS, BRAF, EGFR)
- Additional low-frequency mutations (PTEN, AKT1, ...)

A New Molecular Classification?

Molecular Classification of Breast Cancer

Breast Cancer in 2011

- ER+ HER2-
- HER2+
- ER- HER2-

Breast Cancer in 2016

- ER+ HER2- PIK3CAmt
- ER+ HER2- PIK3CAwt
- ER+ HER2- FGFR1+
- ER+ HER2- BRCA2mt
- ER+ HER2- PIK3CAmt/PTEN-
- ER+ HER2+ PIK3CAwt/PTEN+
- ER- HER2+ PIK3CAmt/PTEN-
- ER- HER2+ PIK3CAwt/PTEN+
- ER+ HER2-
- ER- HER2- BRCA1mt
- ER- HER2- FGFR2+

Adapted from Fabrice Andre
Targeted Therapy?

- Targeting one (or a few) “target genes” is not enough.
- There is extensive cross-talk (positive and negative) among the different biological pathways.
- Inhibition of one gene may activate other gene(s).
- It is necessary to better understand the complexity of human genome.
Ingenuity Pathway Analysis: The “Hubs”
Delta’s domestic route map
Targeted Therapy?

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Circos plot: The new genomic map
The classification of tomorrow?
The complexity of the issue

- Each tumour is different from the others (personalised therapy)
- Tumours change during progression
- There is striking heterogeneity within a given tumour (genetic map of individual tumour cells)
- Is this universe too large to be explored?
Epilogue

- No classification - taken alone - is “perfect”
  - Enthusiasm for the novel assays
  - Biotech pressure

- Clinical, morphological, immunohistochemical and molecular data should be integrated into a single classification scheme with definite prognostic/predictive value