Medical doctors driving medical research, an endangered species in our Flemish universities.

Friday 24 January

Marc de Broe
Master in Medicine

Masters in Medicine: 2005-13: **583** (362-758)

General Practitioners: 32.0%
Specialists: 65.0%
Aspirant-IWT: 3.5%
Medical doctors driving medical research

• **Predoctoral:**
  - FWO-Aspirants, 3yr/3yr
  - IWT-project, funding, wage, 4yr
  - Research Scholarships, 2yr/2yr
  - VIB int. PhD program

• **Pre > Post:**
  - FWO: Clinical Doctorate Grants, 2yr part time to finalize a PhD

• **Postdoctoral:**
  - FWO: Fundamental Clinical Mandate, 5yr/5yr 50%
  - FWO: Postdoctoral Investigator
  - VIB
## Aspirants FWO

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number</th>
<th>Medical Sciences* 26%</th>
<th>Number of MD aspirants**</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>161</td>
<td>42</td>
<td>14</td>
</tr>
<tr>
<td>2006</td>
<td>193</td>
<td>50</td>
<td>16</td>
</tr>
<tr>
<td>2007</td>
<td>209</td>
<td>53</td>
<td>17</td>
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<tr>
<td>2008</td>
<td>203</td>
<td>52</td>
<td>16</td>
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<tr>
<td>2009</td>
<td>211</td>
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<td>52</td>
<td>16</td>
</tr>
<tr>
<td>2011</td>
<td>202</td>
<td>52</td>
<td>16</td>
</tr>
<tr>
<td>mean</td>
<td>197/yr</td>
<td>51/yr</td>
<td>16/yr</td>
</tr>
</tbody>
</table>

* Medical Sciences: Pharmacy, Medicine, Biomedicine

** Stable, notwithstanding decrease in success rate, budgetary reason
Mission and key facts

- Evolution Success Rate

Target: 33%

- Aspiranten
- Postdoctorale onderzoekers
- Onderzoeksprojecten
Instituut Wetenschap Technologie (IWT)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of applicants</th>
<th>Number of MD applicants</th>
<th>Number of successful applicants</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>495</td>
<td>10</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>2010</td>
<td>655</td>
<td>13</td>
<td>6 (42%)</td>
</tr>
<tr>
<td>2011</td>
<td>644</td>
<td>9</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>2012</td>
<td>688</td>
<td>16</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>2013</td>
<td>789</td>
<td>20</td>
<td>1 (5%)</td>
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</tbody>
</table>

Toegepast Biomedisch Onderzoek met een Primair Maatschappelijke Finaliteit
Budget 6,5 milj. Euro
Het TBM-programma wil op lange termijn bijdragen tot de implementatie van nieuwe
therapieën, specifieke preventieve maatregelen en diagnostotechnieken
Vlaams Interuniversitair Instituut Biotechnologie (VIB)

- **International PhD program since 2007**
- **Out of 8 selected young investigators 1 MD**
- **Six out of the 78 research team leaders are MD PhD’s.**

Source: B Fiems, VIB, Januari 2014

Onderzoeksmandaten - Research Scholarships (UA)

- 5-7 new mandates/year, not enough MD candidates

Source: G Verwimp, Januari 2014
Input of MD’s into biomedical research is “limited”
Starters  3.5% of graduates in MM
IWT-VIB marginal

Too short, clinical pressure still remains

How to replace a well functioning staff member can be a problem.

General Practitioners: 32.0%
Specialists: 65.0%
Aspirant-IWT: 3.5 % (+/- 20 /year) Input of MD’s in Biomedical Research is “LIMITED”
Kidney International
Impact Factor 7.95 (2012)

Number of papers per million population 2000-2011

<table>
<thead>
<tr>
<th>Country</th>
<th>Millions of Inhabitants</th>
<th>Manuscripts pmp</th>
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<tr>
<td>Netherlands</td>
<td>16.7</td>
<td>10.6</td>
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<tr>
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<td>11.0</td>
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<td>Denmark</td>
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<td>1.3</td>
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Kidney International
accepted papers from 2000 to 2011
according to first or last author
countries > 1.0 pmp
Nature Medicine
Impact Factor 24.03 (2012)

Number of papers per million population 2000-2011

<table>
<thead>
<tr>
<th>Country</th>
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<th>Manuscripts pmp</th>
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<td>Lebanon</td>
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<td>New Zeal.</td>
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Nature Medicine
papers from 2000 to 2011
according to first or last author
countries > 0.2 pmp
- Countries with well developed PhD program in medicine/biomedicine
- Not very well developed PhD program in medicine/biomedicine
- Countries with emerging research in biomedicine
Kidney Int + JASN rank order

1. USA
2. Canada
3. Australia
4. 5.
5. 11.
6. 8.
7. 10.
8. 9.
9. 2.
10. 3.

Countries with well developed PhD program in medicine/biomedicine
Not very well developed PhD program in medicine/biomedicine
Countries with emerging research in biomedicine
Nature Medicine rank order

Countries with well developed PhD program in medicine/biomedicine
Not very well developed PhD program in medicine/biomedicine
Countries with emerging research in biomedicine

USA  2
Canada  4
Australia  8
The Netherlands

- 165 nephrologists - 30% in university hospitals
- Until recently (still majority) – nephrologists – PhD
- 3-5 papers in peer reviewed journals with high impact factor (6 best journals in nephrology), three as first author;
- Research funding
  - NWO – fundamental research – predoc, postdoc
  - diabetes, rheuma, ...
  - faculties – postdoc for clinicians
  - hospital clinical research
  - EC
  - NIH, others
  - Nederlandse Vereniging Nefrologie – multicenter trials
Nierstichting The Netherlands

Total income 2006: $15 \times 10^6 \text{ €}
75\% spent in research support

2012 : $17.9 \text{ milj Euros}

<table>
<thead>
<tr>
<th>INCOME (thousands of euros)</th>
<th>EXPENSES (thousands of euros)</th>
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<tbody>
<tr>
<td>Collection</td>
<td>4548</td>
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<tr>
<td>Mailing actions</td>
<td>5286</td>
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<tr>
<td>Legacies</td>
<td>4065</td>
</tr>
<tr>
<td>Gifts</td>
<td>268</td>
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<tr>
<td>Assoc. friends</td>
<td>488</td>
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<tr>
<td>Sponsoring</td>
<td>287</td>
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<tr>
<td>Consortia (3 centra)</td>
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<tr>
<td>Innovative grants</td>
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<tr>
<td>Kolff program</td>
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Extracted from: De Nierstichting
Ter Wee personal communication 2012
Number of MD’s starting a research career in Flanders is limited and is decreasing.

Biomedical research in Belgium/Flanders is competitive and remains so/improving over the last 10 years due to better funding and input from non-MD’s trained in biomedicine.

FWO is far out the best provider/controller of the current clinical research mandates for MD’s
The number, quality, and coverage of randomized controlled trials (RCTs) in internal medicine

Number of randomized controlled trials published in nephrology and 12 other specialties of internal medicine from 1966-2010
% growth/decline clinical trial participation

- **US**: Light blue bars
- **EUR**: Dark blue bars
- **NL**: Green bars
- **East EUR**: Red bars
- **ASIA**: Light purple bars
Clinical trials in top journals 2010
The Lancet
Articles pmp, 1998 – July 2004

2009–2013
analogue distribution
Clinical Research (CR) Investigator (MD PhD) Driven

- **Human resources**
  - Number of masters in medicine; increase in number of masters in biomedical sciences
  - Decrease of number of MDs research line career
  - Work load in clinical departments - budgetary pressure
  - Absence of stable long term career in CR
  - Wage difference clinical -- biomedical research career

- **Teaching – organization**
  - Insufficient teaching of CR at master MS level
  - Insufficient funding and lack of infrastructure
  - Increase in guidelines – administrative burden
  - Monopoly of pharma industry in CR – Cost of RCTs
  - Export of CT’s – developing countries
Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis EVOLVE
The EVOLVE Trial Investigators
Cost; 140 million US Dollar (internal resources not included)
In an unadjusted intention-to-treat analysis, cinacalcet did not significantly reduce the risk of death or major cardiovascular events in patients with moderate-to-severe secondary hyperparathyroidism who were undergoing dialysis

BONAFIDE RMP study
Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism (multicenter study)

Cost : 3.5 million US Dollar
RMP: risk management plan (FDA-EMA)
PHARMA INDUSTRY

• The Truth about the Drug Companies. How they deceive us and what to do about it
  
  Marcia Angel  Random House  2004

• Doubt is their Product. How industry’s assault on science threatens your health
  
  David Michaels  Oxford University Press  2008

• Bad Pharma. How drug companies mislead doctors and harm patients
  
  Ben Goldacre  Fourth Estate  2012
Pharma industry (PI)

clinical research “non transparent”

- Trial focus: registration – dominance of PI (85-95%)
- Unappropriate comparisons – doses – too high – too low
- Changing, primary—secondary, irrelevant end points
- Most trials are “me too” – “add on” – no “stop trials"
- Selection of normal subjects – aging? real life setting
- Commercialization of clinical trials (CRO*)
- “Education” of MDs, patient organization,
- Scientific boards, advisory boards
- Export of CR to developing countries

* Contract Research Organization
In a trend that has received little attention contract research organizations (CRO’s) have gradually taken over much of academic role of drug development.

US 30,000/patient
Romania 3,000/patient
CEO Quintiles 2013
Pharma industry – clinical trials

LACK of TRANSPARENCY

• Publication of positive results 70-85%
  • Constraints on publication rights
  • Ghost writing – redundancy – disaggregation

• Negative results <25% published

• Missing data – meta analysis – golden standard?

• Medical journals reprint business

• Regulators should have all the data, often don’t share it

NEED for INVESTIGATOR DRIVEN INDEPENDENT CT (RCT’s) to FORM a COUNTERBALANCE to PHARMA-INDUSTRY
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (1996-2004) NIH Clinical Center

• The study tried to find which was the best choice for starting treatment. Results show that diuretics work best to both lower blood pressure and prevent stroke and some forms of heart disease, including heart attack and heart failure. calcium channel blocker, an angiotensin converting enzyme (ACE) inhibitor, and an alpha-adrenergic blocker.

• In people with diabetes, diuretics work as well as ACE-inhibitors and calcium channel blockers in protecting against heart attack and improving survival, and offer more protection against congestive heart failure.

• The latest findings from the "Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial" or ALLHAT, sponsored by the National Heart, Lung, and Blood Institute, are published in the June 27 issue of Archives of Internal Medicine.
Fewer people should take medicine to control their high blood pressure, a new set of guidelines recommends. *JAMA* Editorial: "Recommendations for Treating Hypertension: What Are the Right Goals-Purposes (jama.jamanetwork.com) (Dec. 18, 2013)

Adults aged 60 or older should only take blood pressure medication if their blood pressure exceeds 150/90, which sets a higher bar for treatment than the current guideline of 140/90, according to the report, published online Dec. 18 in the *Journal of the American Medical Association*.

Review of “quality selected” RCT ‘s of the last 10 years
Investigator driven unrelated to pharma -industry

Endless protest ..........
WHAT CAN and SHOULD WE DO?

• Improve teaching of clinical research – clinical pharmacology

• Create part and full time, long term, clinical research careers for qualified MD’s, competitive wages

• Funding at national, preferably at EU level of clinical research centers (US, UK…)

• Balance between clinical oriented investigator driven research and contract research (pharma-industry …)

• Simplify regulatory bureaucracy, new EU regulations

• TRANSPARENCY

• NICE, Damocles, Sunshine act, ProPublica, NICE, Clinical Trial.gov;

• Examples of potential funding: De uitbouw van het translationeel onderzoek in Vlaanderen 2008
  
  • Centrum voor Medische Innovatie 2009
  
  • Commissie Wetenschappelijk Onderzoek KAGB 2008 2014
TWO REALISTIC PROPOSALS ---- 2014

“HUMAN RESOURCES “

• -- Fundamental Clinical Research Mandates FWO

• -- Clinical Research Centers

• clinical pharmacology

• Internationale Benchmarking van de Financiering van Translationeel Onderzoek 2008 W Luyten

Too short, clinical pressure still remains

How replace a well functioning staff member?

1 -- FKM’s as a career, preferably 50%, evaluation procedure after 3 years

2 -- Increase the number of FKM’s
CLINICAL RESEARCH CENTERS

CLINICAL PHARMACOLOGY

INVESTIGATOR DRIVEN NOT INDUSTRY SUPPORTED CLINICAL RESEARCH

- Faculty of medicine- University hospital supported (RUG, UA, VUB, KUL)
- Multitask - teaching at graduate –post graduate level of CR
  - ethical committee, clinical rounds
  - protocol development, methodology, analysis, storage of data,
  - logistic support, follow up, publication, administration
- RCT’s investigator driven
- industry supported clinical trials drugs ..... devices

COUNTERBALANCE for the monopoly pharma-industry

Upgrade of the important aspect of patient related Clinical Research
Thanks
Probiotica

Medicijnproef eist liefst 24 levens

donderdag 24 januari 2008 | 03:32 | Laatst bijgewerkt op: donderdag 14 februari 2008 | 20:09

The NEW ENGLAND JOURNAL of MEDICINE

2007

Effects of Torcetrapib in Patients at High Risk for Coronary Events

Death from Any Cause

34 more deaths in intervention group
(9 in Netherlands)

Tissue plasminogen activator

Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial

A assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary intervention (ASSENT-4 PCI) investigators

21 more deaths in intervention group

Logrank test: p=0.1187

Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial

Parasympathicomimeticum

Lancet 2010