Drug Discovery and Development

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VIB, 1 March 2018
What is?

**drug**
/nɔr\d/\n
**noun**
1. a medicine or other substance which has a physiological effect when ingested or otherwise introduced into the body.
    "a new drug aimed at sufferers from Parkinson's disease"
    synonyms: medicine, medication, medicament, pharmaceutical; More

**verb**
1. administer a drug to (someone) in order to induce stupor or insensibility.
    "they were drugged to keep them quiet"
    synonyms: anesthetize, narcotize; More

Trastuzumab (Herceptin)

Other:
- Antibody-small molecule conjugates
- Vaccine
- Polynucleotides (aptamers)
- RNAi
- Bacteria - microbiome
- nanomaterials
- gene therapy/editing

Esomeprazole (Nexium)

small molecule (H+/K+ ATPase antagonist)

large molecule
Biological (erbB-2 antagonist)
275 New approved drugs 1998-2007

- 215 small molecule (NDA: New Drug Application)
- 60 biologicals (incl polypeptide/nucleotide) (BLA: Biological License Application)

Robert Kneller
Nature Reviews Drug Discovery 9, 867-882 (November 2010)
New Drug Approvals over the past 25 years

Nature Reviews Drug Discovery
15: 73 (2016)

Figure 1 | Novel approvals since 1993. New molecular entities (NMEs) and Biologics License Applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER) since 1993. Approvals by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count. Data are from Drugs@FDA and the FDA.
2015 New Drug Approvals

A neprilysin inhibitor plus an angiotensin II receptor blocker
Chronic heart failure

CDK4 and CDK6 inhibitor
ER-positive, HER2-negative advanced breast cancer

CFTR potentiator plus CFTR corrector
Cystic fibrosis in patients with homozygous ΔF508 CFTR mutation
From molecule to medicine
High Risk, Huge Investment

⚠️ AVERAGE COST OF FULL DEVELOPMENT OF ONE MEDICINE: €1,250,000,000

⚠️ AVERAGE TIME TO DEVELOP ONE MEDICINE: 14 YEARS

BEGIN: 10,000 MOLECULES
100 discovery projects

On average 6 years to sell product before drug becomes generic
Pharma Productivity

The Cost Of Creating A New Drug
Now $5 Billion, Pushing Big Pharma
To Change

March 10, 2016
Tufts CSDD Assessment of Cost to Develop and Win Marketing Approval for a New Drug Now Published
BOSTON – March 10, 2016 — The most recent analysis by the Tufts Center for the Study of Drug Development of the average cost to develop and gain marketing approval for a new drug—pegged at $2.566 billion—has been published in the Journal of Health Economics. It was announced today.

BUT:
R&D productivity:
on the comeback trail
Nature Rev Drug Disc 2014

Discovery of Innovative Therapeutics: Today’s Realities and Tomorrow’s Vision. 2. Pharma’s Challenges and Their Commitment to Innovation
Magid Abou-Gharbia* and Wayne E. Childers
J Med Chem 2014
## From molecule to medicine

<table>
<thead>
<tr>
<th>Basic Research/Discovery</th>
<th>Development</th>
<th>Clinical Trials</th>
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<tbody>
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<td>- Select Disease(s)</td>
<td>- Drug metabolism and Pharmacokinetics</td>
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<td>- Identify Bioassay</td>
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<td></td>
<td></td>
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<td>- Select clinical candidate</td>
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**Timeline:**
- 0 YEAR
- 4 YEAR
- 6 YEAR
- 12.5 YEAR
- 14 YEARS
- 20 YEAR

**Process Overview:**
- **Basic Research/Discovery**
  - Select Disease(s)
  - Select Drug Target
  - Identify Bioassay
  - Find compound hits
  - Find lead compound(s)
  - Select clinical candidate

- **Development**
  - Drug metabolism and Pharmacokinetics
  - Safety evaluation
  - Chemical production
  - Pharmaceutical formulation

- **Clinical Trials**
  - Safety (Phase I)
  - Efficacy & Dose (Phase II)
  - Efficacy (Phase III)
  - Postmarketing (Phase IV)

**From Discovery of a Drug to Submission of Registration File:**
- Begin: 10,000 molecules
- End: 1 New Medicine
1. Select Disease(s)

• Pharmaceutical companies are commercial enterprises and will, therefore, mostly focus on diseases with large enough expected market

• Most pharma research is done on diseases which afflict “first world” countries: (e.g. cancer, cardiovascular diseases, autoimmune diseases, neurodegeneration, depression, diabetes, flu, migraine, obesity)

• The Orphan Drug Act of 1983 encourage pharmaceutical companies to develop drugs to treat diseases which affect fewer than 200,000 people in the US: entitled to market it without competition for seven years

• Priority Review Voucher system: company develops drug for neglected disease -> voucher allows company to fast-track another drug candidate
Pharma companies focus on a limited number of diseases
Biotech often on one or two

Areas of interest
Across our biologics and small molecule research, we are concentrating our scientific efforts and the weight of our investment, including business development, on three core therapy areas:

- Cardiovascular & Metabolic Disease (CVMD)
- Respiratory, Inflammation & Autoimmune (RIA)
- Oncology

Alongside this, we remain active in Infection and Neuroscience with targeted investments in the best opportunities and collaborations.

- Infection
- Neuroscience

December 6, 2011 [http://blog.sciencemag.org/]

Novartis: No More Neuroscience

Posted by Derek

Neuroscience is a long-established graveyard for drug discovery - the

Pharma giant Pfizer pulls out of research into Alzheimer's

© 10 January 2018
New Drugs per therapeutic area

Distribution of NMEs (New Molecular Entities) across therapeutic areas (2000–2012)

Munos, Clinical Pharmacology & Therapeutics (2013); 94, 407–411
New Drug Approvals in 2015 by therapeutic area

Nature Reviews Drug Discovery
15: 73 (2016)
2. Select Target
(or select target agnostic phenotypic assay)

- Drug Target = specific macromolecule, or biological system, which the drug will interact with

**BRAF as a potential therapeutic target in melanoma and other malignancies**

David A Tovesson, Barbara L Webber, Moonhard Hestyan

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**Systems genetics for drug target discovery**

Nadia M. Perroud, Richard Cowper-Silber, Jason H. Moore

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**The Telomeric Protein TRF2 Regulates Angiogenesis by Binding and Activating the PDGFRβ Promoter**

Mount El Mol, Kay-Dietrich Wagner, Jean-François Michiels, Damien Amorimetti, Arnaud Bordenie, Sandrine Destree, Valente Rambaut, Nadir Efjorg, Marie-Joseprie Giraud-Paris, Eric Gibson, Nicole Wagner

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**Eps8 regulates cellular proliferation and migration of breast cancer**

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**Authors**: Cheng Chen, Zhongheng Liang, Wenhuan Huang, Xin Xin Li, Fangliang Zhou, Xiang Hu, Mei Han, Xiaofeng Ding, Shuanglin Xiang

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**GWAS and drug targets**

Chen Cao, John Moul

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**Original Article**

B-myb is a gene implicated in cell cycle and proliferation of breast cancer

Deyou Tao, Yihong Pan, Hongzheng Lu, Song Zhong, Hui Lin, Hongyan Faeng, Feilin Cao
Targets are elements of cellular pathways
### New Drugs per target class (2000-2012)

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine kinase inhibitor</td>
<td>17</td>
</tr>
<tr>
<td>Enzyme replacement therapy</td>
<td>12</td>
</tr>
<tr>
<td>Vaccine</td>
<td>7</td>
</tr>
<tr>
<td>Protein replacement therapy</td>
<td>6</td>
</tr>
<tr>
<td>Bacterial cell wall synthesis inhibitor</td>
<td>5</td>
</tr>
<tr>
<td>DNA synthesis inhibitor</td>
<td>5</td>
</tr>
<tr>
<td>Bacterial protein synthesis inhibitor</td>
<td>4</td>
</tr>
<tr>
<td>GABA analog</td>
<td>4</td>
</tr>
<tr>
<td>Histamine release inhibitor</td>
<td>4</td>
</tr>
<tr>
<td>HIV protease inhibitor</td>
<td>4</td>
</tr>
<tr>
<td>M3 muscarinic acetylcholine antagonist</td>
<td>4</td>
</tr>
<tr>
<td>Ovulation suppression</td>
<td>4</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>4</td>
</tr>
<tr>
<td>D2/5-HT2A antagonist</td>
<td>3</td>
</tr>
<tr>
<td>5-HT1B/1D agonist</td>
<td>3</td>
</tr>
<tr>
<td>Acetylcholine-release inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Direct thrombin inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>DPP4 inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Ergosterol synthesis inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Erythropoietin receptor activator</td>
<td>3</td>
</tr>
<tr>
<td>Glucan synthase inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>GnRH antagonist</td>
<td>3</td>
</tr>
<tr>
<td>HBV DNA polymerase inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Mitotic inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Osteoclast inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Serotonin and norepinephrine reuptake inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>TNF-α blocker</td>
<td>3</td>
</tr>
<tr>
<td>μ-Opioid antagonist</td>
<td>2</td>
</tr>
<tr>
<td>5-HT3 antagonist</td>
<td>2</td>
</tr>
<tr>
<td>Acetylcholinesterase inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Angiogenesis inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonist</td>
<td>2</td>
</tr>
<tr>
<td>Antiviral</td>
<td>2</td>
</tr>
<tr>
<td>Apoptosis inducer</td>
<td>2</td>
</tr>
<tr>
<td>Bronchodilator</td>
<td>2</td>
</tr>
<tr>
<td>C1 esterase inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Cofactor of thrombin activation cascade</td>
<td>2</td>
</tr>
<tr>
<td>Conjugated immunotoxin</td>
<td>2</td>
</tr>
<tr>
<td>Conjugated radioimmunotherapy</td>
<td>2</td>
</tr>
<tr>
<td>CTLA4-1g agonant</td>
<td>2</td>
</tr>
<tr>
<td>D2/5-HT2A antagonist</td>
<td>2</td>
</tr>
</tbody>
</table>

Munos, Clinical Pharmacology & Therapeutics (2013); 94, 407–411
Targets of all marketed drugs (2006)
## Targets of all marketed drugs and clinical candidates (2014)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplored proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical trial drug-target proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established drug-target proteins</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Annu. Rev. Pharmacol. Toxicol. 54:9–26
Druggable genome


Griffith et al
Nat. Meth. 10:1209 (2013)
3. Identify the Bioassay

• Assays can be with purified target, in cell preparations, living cells, living organisms
• Functional and binding assays
• Phenotypic assays: target agnostic
• Primary and secondary/orthogonal assays

- High content cellular imaging
- Zebrafish behavior
- Surface plasmon resonance (SPR)
- Alphascreen
4. Find Hits

- Screening of compound libraries in primary assay
  - Company collections (~ 1-5 million)
  - Commercially available (www.emolecules.com)
  - Natural products
  - Target class specific libraries (e.g. kinases)
  - Combinatorial chemistry – DNA encoded libraries (billions of molecules)
- Public screening centers
  - European Lead Factory (http://www.europeanleadfactory.eu/)
  - European ScreeningPort (http://www.screeningport.com/)
Fragment Based Lead Discovery (FBLD)

- Fragments are smaller than usual screening compounds and tend to have lower affinity (mM-uM) and need to be expanded or linked to get to required affinity (usually nM)
- Key value is the Ligand Efficiency (LE), the binding energy per atom
  \[
  LE = \Delta G / \#\text{nonHatoms} = -1.4 \times \log(\text{IC50}) / \#\text{nonHatoms}
  \]
  (good value is >0.45)
- See http://practicalfragments.blogspot.be/ for examples and new developments

http://www.creative-biostructure.com
A (new) option: PROTACs

- Proteolysis-targeting chimaera (PROTAC)
- Target proteins are ubiquitinated and degraded in proteasome
- Multiple E3 ligase ligands are available
- Interesting for:
  - Targets without druggable active site
  - Need to reduce levels of Protein of Interest (POI)

Figure 5. A small-molecule PROTAC that recruits the MDM2 E3 ligase.
5. Find Lead Compound(s)

Design – Make – Analyze – Test cycle
5. Find Lead Compound(s)

Hit to Lead and Lead Optimization are multi-parameter optimizations
- Activity, Selectivity, ADME (absorption, distribution, metabolism, excretion), Patents, Physico-chemical properties, Toxicology, etc
- Hit to Lead phase: improve properties for several chemical series to acceptable level
- Lead Optimization phase: focus on one or a few series to optimize to a clinical candidate

[Diagram of the triage plan process]

http://services.medicine.uab.edu/publicdocuments/peds/adda/121005_Med_Chem.pdf
During Hit to Lead and Lead Optimization thousands of compounds are synthesized.

Table 2. Introduction of Water Solubilizing Groups To Improve Solubility

<table>
<thead>
<tr>
<th>Compd</th>
<th>Structure</th>
<th>Solubility (μM)</th>
<th>P1 IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH 2 (STD)</td>
<td>pH 6.5 (STD)</td>
<td>KI</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>188 (2.7)</td>
<td>157 (4.1)</td>
</tr>
<tr>
<td>17</td>
<td>&gt;200</td>
<td>&gt;100</td>
<td>78</td>
</tr>
<tr>
<td>21</td>
<td>190 (8.2)</td>
<td>8.6 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>2.6</td>
</tr>
<tr>
<td>23</td>
<td>&gt;200</td>
<td>178 (1.1)</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td></td>
<td>166 (8.8)</td>
<td>162 (0.4)</td>
</tr>
<tr>
<td>32</td>
<td>207 (1.2)</td>
<td>98 (1.6)</td>
<td>-</td>
</tr>
<tr>
<td>35</td>
<td>191 (0.8)</td>
<td>177 (11)</td>
<td>21</td>
</tr>
<tr>
<td>36</td>
<td>&gt;200</td>
<td>180 (7.5)</td>
<td>9.4</td>
</tr>
<tr>
<td>37</td>
<td>112 (7.5)</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>40</td>
<td>205 (1.3)</td>
<td>192 (2.4)</td>
<td>30</td>
</tr>
</tbody>
</table>

SAR table:
structure-activity relationships
Computational Drug Design

• Design, select, or evaluate molecules for better drug properties, using computer technologies for analysis
• Broadly speaking, there are two important approaches
  – Ligand-based methods: using information on known active and inactive molecules
  – Protein structure based methods: using the 3D atomic structure information of the protein target
Ligand-based methods

Activity data of molecules

Statistical predictive model

3D model of important features: pharmacophore
Structure based methods

Free Energy calculations: predicting the relative free energy of binding between molecules

Molecular docking and design
Lead optimization: in vivo proof of concept

Adenovirus–Retrovirus Hybrid Vectors Achieve Highly Enhanced Tumor Transduction and Antitumor Efficacy In Vivo (introduction of Cytosine deaminase gene converts 5-FC to 5-fluoro-uracil, an antitumor drug)

Molecular Therapy (2011) 19 1, 76–82
Hybridoma is a hybrid cell used as the basis for the production of antibodies in large amounts. They are produced by injecting a specific antigen into a mouse, collecting an antibody-producing cell from the mouse's spleen, and fusing it with a tumor cell called a myeloma cell.

Start: target is defined

antigen=target

Lead Molecule is defined

End of development, ready for clinical studies

http://www.genscript.com/therapeutic_antibodies.html
Phenotypic Drug Discovery: not focused on target assay, but on “phenotypic assay”

## From molecule to medicine

### Basic Research/Discovery
- Select Disease
- Select Drug Target
- Identify Bioassay
- Find compound hits
- Find lead compound(s)
- Select clinical candidate

### Development
- Drug metabolism and Pharmacokinetics
- Safety evaluation
- Chemical production
- Pharmaceutical formulation

### Clinical Trials
- Safety (Phase I)
- Efficacy & Dose (Phase II)
- Efficacy (Phase III)
- Postmarketing (Phase IV)

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**Timeline:**
- **0 YEAR**
- **4**
- **6**
- **12.5y**
- **14 YEARS**
- **20y**

**Stages:**
- Basic Research
- Development
- Clinical Trials
- Registration
- Commercialization

**From discovery of a drug to submission of registration file:**

**From registration to launch:**

**From launch to loss of patent:**

**Begin:** 10,000 molecules

**End:** 1 new medicine
• Safety & toxicity in animals

• Acute toxicity profile
• Chronic toxicity profile
  – 14 day toxicity test in one rodent and one non-rodent species before use in man
  – 3 month study read out at 28 days
  – Longer studies (12 & 24 month)
• Three dose levels (below, about, well above human dose)
• It is insufficient to use doses which are not toxic; the doses producing toxic effects and the nature of these effects MUST be established.
• Formulation studies

• DRUG (active pharmaceutical ingredient API) + Additive: filler, lubricant, coating, stabiliser, color, binder, disintegrator

Dosage form: capsule, tablet, injection, other?

Manipulate duration/profile: e.g. sustained release
• Clinical testing

• Phase 0 (volunteers, subtherapeutic)
• Phase 1 (volunteers)
• Phase 2 (patients)
• Phase 3 (large scale multi-center)
• Phase 4 (post registration monitoring)
Volunteer studies (phase I trials)

- healthy pharmacologists, employees, other (15-30 in number)
- ethical approval, informed consent
- medical backup, monitor
- single and repeat doses, increase dose levels

OBJECTIVES
- metabolic and excretory pathways (depends on toxicity testing in animals)
- variability between individuals; effect of route; bioavailability
- tolerated dose range
- indication of therapeutic effects (sometimes)
- indication of side effects
Patient studies (phase 2 trials)

• 150-350 ill people; informed consent
• needs license
• maximum monitoring
• often patients where other treatment failed
• OBJECTIVES:
  – indication for use; type of patient; severity of disease;
  – dose range, schedule and increment;
  – pharmacokinetic studies in ill people;
  – nature of side effects and severity;
  – effects in special groups.
Patient studies (phase 3 trials)

- 1500-3500 ill patients
- often randomized double blind studies
- often multicenter
- more certain data for the objectives of phase 2 studies
- interactions between drugs start to become measurable in the larger population
- sub-groups start to be established
- special features and problems show up
Drug Discovery Case History: denosumab (Prolia®, Xgeva®)

- denosumab: monoclonal antibody to RANKL, approved for use in both postmenopausal osteoporosis and oncology
Timeline | Development of Amgen's RANKL inhibitors

1997–1998:
- Identification and cloning of RANK and RANKL
- A molecule that binds to OPG is identified and referred to as OPGL; it is found to be identical to RANKL; OPG is thus recognized as a decoy receptor
- Seminal role of RANK–RANKL pathway in osteoclast biology is defined
- Numerous OPG variants are explored preclinically for potential clinical trials
- Fc–OPG enters clinical testing

1999–2001:
- OPG–Fc enters clinical testing
- Denosumab (AMG 162), a fully human anti-human RANKL mAb is identified during the XenoMouse campaign at Abgenix
- First dose of denosumab is administered in humans on 30 June 2001

2006–2009:
- Phase III SRE denosumab trials are initiated in advanced cancer
- Key denosumab postmenopausal osteoporosis and CTIBL clinical studies are completed and published

2010–2011:
- Prolia (denosumab 60 mg Q6M) receives regulatory approval for treatment of postmenopausal women with osteoporosis who are at a high risk for fracture, and is later approved for treatment to increase bone mass in men with non-metastatic prostate cancer receiving ADT who are at high risk for fracture as well as in women with breast cancer receiving aromatase inhibitor therapy who are at high risk for fracture
- Long-term data are reported from a Phase II study, representing 8 years of continuous denosumab treatment in postmenopausal women
- Key denosumab SRE clinical studies are completed and published
- Xgeva (denosumab 120 mg Q4W) receives regulatory approval for the prevention of SREs in patients with bone metastases from solid tumours
- Positive data are released demonstrating that denosumab (120 mg Q4W) increases bone-metastasis-free survival in men with castration-resistant prostate cancer

OPG is disclosed in patent filings as an important regulator of bone density

ADT, androgen deprivation therapy; CTIBL, cancer treatment-induced bone loss; mAb, monoclonal antibody; OPG, osteoprotegerin; OPGL, OPG ligand; Q4W, dose administered every 4 weeks; Q6M, dose administered every 6 months; RANK, receptor activator of NF-κB; RANKL, RANK ligand; SRE, skeletal-related event.
RANK, RANKL, OPG

3D structure RANKL

Bone formation
Osteoprotegerin (OPG) is a decoy receptor for the “receptor activator of nuclear factor kappa B ligand” (RANKL)

- OPG can reduce the production of osteoclasts by inhibiting the differentiation of osteoclast precursors
- denosumab also binds RANKL and therefore reduces RANKL-RANK interaction, leading to reduction in osteoclast differentiation
Multiple approaches for lead molecules

Q: How to reduce RANKL levels?

(These are all engineered protein constructs)
Monoclonal Antibody (mAb) developed using XenoMouse

• XenoMouse technology generates antibodies with human sequences in mice (technology developed at Abgenix; use of mouse embryonic stem cells)

• Antibodies were tested for activity and binding kinetics using surface plasmon resonance (SPR, Biacore™)

• AMG 162 antibody was selected because it was a strong inhibitor of RANKL-induced osteoclast formation, and later named denosumab
In vivo Pharmacology

- denosumab does not bind rodent RANKL, and preclinical in vivo test had to be done on cynomolgus monkeys (efficacy and safety)

OVX: ovariectomized
Dmab-25/50: denosumab at 25 or 50 mg/kg every 4 weeks

White arrow: cortical pore in rib
RANKL inhibition: also for cancer

- RANKL inhibitors reduce tumour-induced osteolysis (sign of bone metastasis) in breast, lung, prostate and colon cancers as well as in rodent models of multiple myeloma.
- RANK-RANKL was shown to also play a role in breast cancer, and inhibition by RANK-Fc blocked tumor formation in mice.

Kaplan-Meier survival curves
Clinical trials

• In 2001 Amgen started clinical trials of denosumab in patients with osteoporosis, cancer treatment-induced bone loss in early-stage cancer and cancer-induced bone destruction in advanced cancer

• The ability of denosumab to reduce levels of markers of bone turnover in humans was demonstrated in a single dose Phase I trial in healthy postmenopausal women
Clinical Trials

• In a Phase II study, a total of seven doses and two dosing schedules (administration every 3 months (Q3M) and every 6 months (Q6M)) of denosumab were evaluated at the 1-year primary end point.

• The 60 mg Q6M dose was selected for the Phase III studies because it was the lowest dose at the least frequent interval that achieved the maximal gain in BMD (bone mineral density).
Phase III results

PMO: postmenopausal women with osteoporosis
CTIBL: cancer treatment-induced bone loss

Denosumab: approved by FDA in 2010
Commercial names:
- Prolia (60 mg subcutaneous (sc) every 6 months)
- Xgeva (120 mg sc every 4 weeks)
Drug Discovery Case History: rivaroxaban (Xarelto®)

- Small molecule Factor Xa inhibitor for use as an anti-coagulant
Links

• Interesting web sites on pharmaceutical research
  – http://blog.sciencemag.org/ (Derek Lowe blog)

• Videos explaining drug discovery
  – https://www.youtube.com/watch?v=d9ouk_46xA8 (Short film on drug discovery)
  – https://www.youtube.com/watch?v=KQKppAAR3ME (UCSF part 1)
  – https://www.youtube.com/watch?v=K9jfvCAPghs (UCSF part 2)

• Nature Reviews in Drug Discovery
  – Discovery Tech http://www.nature.com/nrd/series/drugdiscovery/index.html
  – Drug case studies http://www.nature.com/nrd/series/casehistories/index.html