Rare Diseases and Orphan Drugs

Overview
• An orphan drug (OD) is a pharmaceutical agent developed for the treatment of rare medical conditions
• Criteria for a rare disease (for orphan drug designations)
  - FDA: less than 200,000 people affected in the US (about 6 cases per 10,000 population)
  - EU: less than 1 case in 2000 population; symptoms must be life-threatening or chronically debilitating
  - Similar requirements from other countries (e.g. Australia, Japan, Singapore)
• Without incentives, development of orphan drugs is almost never profitable
  - The Kefauver-Harris Bill (1963) requires all drugs to be proven safe and effective before approval for US market
  - Increasing cost of drug development funnels interest towards common diseases
• Only 38 would-be orphan drugs approved by FDA before 1983

The Orphan Drug Act (ODA) of 1983
• Crucial lobbying efforts from National Organization of Rare Disorders (NORD) and other patient advocacy groups
• Public awareness was raised in 1981 when “Quincy, M.E.” (starring Jack Klugman) dedicated episodes to rare diseases
  - Klugman later testified before the Congress regarding orphan drug issues
• In 1983 the ODA was passed and signed by Ronald Reagan
• Incentives include:
  - 7 year market exclusivity
  - Up to 50% of development cost reimbursed as tax credits (later amended to a 15-year provision package)
  - Drug development grants
  - Fast-track approval at FDA
  - Expanded access to Investigational New Drug Program (allows patient access to pre-approved orphan drugs)
  - FDA drug application fee waived
• 7-year market exclusivity is extremely appealing to pharmas
  - Begins upon FDA approval, not the beginning of clinical trials
  - Independent of the drug’s current patent status
  - Competing drug candidates need to be proven superior
  - Essentially creates an “ideal” monopolistic market
• Less rigorous clinical trial requirements for orphan drugs
  - Fewer tests on patients = lower cost & less time

Follow-up Legislations
• The Rare Diseases Act was passed and signed in 2002
  - Establishes the Office of Rare Diseases under NIH
• The Rare Diseases Clinical Research Network (RDCCRN)

Some useful resources:
• FDA website, “developing products for rare diseases”

Global statistics of orphan drugs
• Worldwide OD sales in 2020: $140 billion
  - About 15% of the entire prescription drug market
• 31 out of 53 FDA approved drugs in 2020 acquired orphan designations (58%)
• Top 3 companies with highest worldwide OD sales in 2018:
  - Celgene ($12.6 billion)
  - Roche ($10.3 billion)
  - Novartis ($10.2 billion)
• Market is rapidly changing: BMS ($3.8 billion in 2018) projected to achieve $16.6 billion OD sales in 2024, overtaking the current top three (due to acquisition)
• Companies that specialize in orphan drugs have emerged:
  - e.g. Vertex Pharmaceuticals, Alexion Pharmaceuticals, etc.

Problems of orphan drug development & market
• Hyperinflated drug prices
  - Spinraza (Biogen): $125,000 per injection, $750,000 in the 1st year
  - Ivacaftor (Vertex Pharmaceuticals): $311,000 per year
• Same-drug problem: how “different” is enough?
  - Protropin (Genentech) and Humatrope (Eli Lilly) differed by ONE amino acid residue
  - Court ruled that the two drugs were different but refused to provide general criteria
• Duration of the OD designation
  - Zidovudine, or AZT, was approved as an orphan drug for HIV treatment in 1987 but maintained its orphan status even after AIDS became a global pandemic
• Is it ethical to develop blockbuster drugs under orphan drug policies?
• Calls for reforms
  - Reduce the duration of market exclusivity
  - Forfeit OD designation if patient number grows beyond 200,000
  - A sales “trigger” that causes the drug to lose orphan designation?

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Case study: Cystic Fibrosis (CF)
- Is a genetic disorder affecting lungs as well as other major organs
- Is autosomal recessive:
  - Caused by mutation in both copies of the CFTR gene on Chr. 7
  - Typical Mendelian inheritance
- Symptoms include:
  - Frequent lung infection
  - Coughing & shortness of breath
  - Mucus accumulation
  - Salty skin (sweat test diagnosis)
  - Poor growth and weight gain

Mechanism of action:
- CFTR protein is a Cl⁻ ion channel protein
  - Pumps Cl⁻ outside of the cell
  - Inhibits ENac, a Na⁺ channel protein that transports Na⁺ inside
- In lung cells, airway surface liquid (ASL) is crucial for the normal function of cilia, which actively moves mucus outward
- When CFTR does not function properly:
  - Excess Cl⁻ is trapped inside the cell
  - ENac activity unregulated = excess Na⁺
  - Build-up of NaCl inside the cell
  - Osmotic pressure forces water inside, resulting in draining of the ASL

- Non-functional cilia = mucus accumulation and leads to other CF symptoms
- In sweat glands, the direction of CFTR is reversed
  - Over-secretion of NaCl
  - Basis of the sweat test diagnosis

Treatment:
- NO CURE for CF is known up to date
- Procedures required if airway is blocked
- Antibiotics needed at all times to prevent any potential lung infection
- Pulmozyme, (Genentech, rhDNase) can loosen mucus and alleviate symptoms
  - Orphan designation granted in 1991

The “trifecta” in CF treatment:
- Developed by Vertex Pharmaceuticals
- FDA approval in 2012 with orphan designation
- Very expensive - over $300,000 per year
- First CF drug that targets the CFTR protein
- Works with patients carrying G551D mutation in the CFTR gene
  - 4% of total patients
- CFTR potentiator: Directly binds to the protein ion channel and promote transport of Cl⁻
Rare Diseases and Orphan Drugs

Case study: Familial Hypercholesterolemia (FH)
- Is a genetic disorder that results in high cholesterol levels in the body
  - Especially low density lipoproteins (LDL, "bad cholesterol")
- Is usually autosomal dominant
  - One copy of defective gene is enough to cause symptoms (in most cases)
  - However, homozygous FH patients experience more severe symptoms and are much more difficult to treat
- Common symptoms include:
  - Cholesterol deposit near eyelids
  - Cardiovascular diseases
  - Heterozygous FH: symptom onset can occur at age 30 to 40
  - Homozygous FH: may cause symptoms as early as childhood

Mechanism of action:
- Most common cause of FH is LDLR mutations on Chr. 19
  - About 1 in 500 people worldwide carries at least one mutated LDLR gene
  - Heterozygous FH is not a rare disease!
  - However, homozygous FH is much rarer (1 in a million)
- LDL receptor proteins in liver are responsible for cholesterol uptake and digestion
  - Regulates blood cholesterol level
- Other FH-causing mutations include ApoB (1 in 1000), PCSK9, and LDLRAP1 (rare)
- Joseph L. Goldstein and Michael S. Brown won the 1985 Nobel Prize in Physiology or Medicine “for their discovery concerning the regulation of cholesterol metabolism”

Treatment:
- Heterozygous FH: can be treated with statin drugs
  - Upregulates functional LDLR proteins to decrease blood cholesterol level
- Homozygous FH: treatment remains challenging
  - Lack of LDLR activity = little to no response to most statin drugs
  - LDL apheresis can temporarily reduce blood cholesterol level (similar to dialysis)
  - Liver transplant necessary for severe cases. Cons: long wait, risk of complications

Both tezacaftor and elexacaftor are CFTR correctors
- Facilitates the correct folding and cell-membrane presentation of defective CFTR proteins
- Elexacaftor/tezacaftor/ivacaftor combination therapy gained FDA approval in 2019 as an OD
- Brand name Trikafta®
- Works with patients carrying at least one F508del mutation in the CFTR gene
  - Covers about 90% of all cystic fibrosis patients
  - List price: $311,000 per year


https://www.britannica.com/science/familial-hypercholesterolemia


Synthesis of fragments:
- EtO₂C₂O₂Et + N₂H₄ → EtO₂C₂O₂Et
- Me₅Bu₃N⁺Cl⁻ → NaOH, CHCl₃ then H⁺
- 1) [Rh(nbd)Cl]₂ MandyPhos 5 bar H₂
- 2) LiAlH₄

Assembly:
- BrN₂F + K₂CO₃ → BrN₂F

OPRD 2019, 2302.
Rosuvastatin: generic or orphan drug?

*Synthesis of pyrimidine core:*

\[
\begin{align*}
\text{F} & \quad \text{Me} \\
\text{O} & \quad \text{Me}
\end{align*}
\]

1) \(\text{NaNH}_2, 70\%\)  
2) \(\text{MeI}, 96\%\)

\[
\begin{align*}
\text{EtO} & \quad \text{iPr} \\
\text{O} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{NMe} \\
\text{O} & \quad \text{NH}_2
\end{align*}
\]

1) \(\text{MsCl}, 91\%\)  
2) \(\text{NBS}, \text{h}\nu, 80\%\)

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\begin{align*}
\text{N} & \quad \text{N} \\
\text{Me} & \quad \text{Ar}
\end{align*}
\]

1) tetraethylammonium fluoride (pyridine)  
2) \(\text{Et}_2\text{BOMe} \quad \text{NaBH}_4\)

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\begin{align*}
\text{F} & \quad \text{O} \\
\text{Me} & \quad \text{O}
\end{align*}
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\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
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\begin{align*}
\text{N} & \quad \text{N} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

- Inhibits HMG-CoA reductase, an enzyme associated with cholesterol production  
- FDA approval in 2003 as a generic drug  
- Gained OD designation in 2014 under AstraZeneca for treating homozygous pediatric FH; exclusivity ends 2023  
- A generic drug can be repurposed towards an orphan market

Selected OD Syntheses:

Tasimelteon (Hetlioz®; Vanda Pharmaceuticals)

- Approved in 2014 with OD status for the treatment of non-24-hour sleep-wake disorder  
- Often occurs in blind people; disrupted circadian rhythms  
- Selective agonist for melatonin receptors MT1 and MT2  
- Controversy: initial OD designation is only for treating blind patients; however, FDA later approved use for all people

Risdiplam (Evrysdi®; Genentech)

- Approved in 2020 for treatment of spinal muscular atrophy (SMA)  
- First oral medication approved  
- Is a mRNA splicing modifier for the \(\text{SMN2}\) gene  
- Defective SMN proteins are the direct cause of SMA  
- Up to 2-fold increase of functional SMN proteins

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\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}
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W.O. Patent: 2015123389A1


W.O. Patent: 9825606A1


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Rare Diseases and Orphan Drugs

Dongmin Xu

Lonafarnib (Zokinvy®, Eiger Biopharma)
- Approved in 2020 for reducing the risk of death for patients with Hutchinson-Gilford progeria syndrome
- Progeria is an extremely rare (less than 1000 cases in the US), autosomal dominant genetic disorder
  - Major symptom: premature aging
  - Typical life expectancy is 10-20 years
  - Severe cardiovascular conditions the major cause of death
- Progeria caused by mutation in LMNA gene
  - Encodes lamin A protein, an important structural protein for the nuclear lamina
  - Defective lamin A (progerin) deforms the nuclear envelope (see right picture)
  - This leads to disruption in the organization of chromatin/chromosomes
  - Result: ability of cell division attenuated
- Lonafarnib is a farnesyl transferase inhibitor
  - Prolamin A undergoes a series of PTMs before being transported to nucleus
    - Farnesylation of a Cys residue
  - Normal: enzymatically cleaved off
  - Progeria: lack of cleavage site results in failed cleavage; farnesylation becomes permanent, and progerin is “stuck” on the nuclear envelop
  - Lonafarnib shuts down farnesylation, thus prevents progerin aggregation at the nucleus
  - Significantly lower mortality rate (3.7% vs. 33.3%) in a 2018 clinical study

Synthesis of lonafarnib:

Glasdegib (Daurismo®, Pfizer)
- Approved in 2018 for treatment of acute myeloid leukemia (AML) with OD status
- Also gained OD designation in 2017 for treatment of myelodysplastic syndrome; clinical trials ongoing
- Is a hedgehog (Hh) signaling pathway inhibitor
  - Hh responsible for stem cell differentiation
  - Often over-activated in cancer cells

“The Oncology Bunch”

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Synthesis of lonafarnib:
Olaparib (Lynparza®, AstraZeneca)
- Approved in 2014 for treating ovarian cancer
- Discovered by KuDoS Pharmaceuticals
  - Acquired by AstraZeneca in 2006

**Med chem route:**
1) (COCl)_2
2) MeNH(OMe)
3) MeMgBr

- Process route is similar to med chem

Alternative route: aminocarbonylation

Capmatinib (Tabrecta®, Novartis)
- Approved in 2020 for treating metastatic non-small cell lung cancer (NSCLC)
- Is a tyrosine kinase inhibitor
  - Inhibits c-Met

**1) Sonogashira**
**2) H_2, Pd/C**
**3) deprotection**
**4) NCS, proline**

- Allows easy radiolabeling with ^13CO / ^14CO

Niraparib (Zejula®, Tesaro)
- Approved in 2017 for maintainence treatment of cancer patients under Pt-based chemotherapy

Selpercatinib (Retevmo®, Eli Lilly, 2020)
- NSCLC

Pralsetinib (Gavreto®, Blueprint Medicines, 2020)
- NSCLC

Pemigatinib (Pemazyre®, Incyte Co., 2020)
- Metastatic bile duct cancer

Avapritinib (Ayvakit®, Blueprint Medicines, 2020)
- Metastatic gastrointestinal stromal tumor (GIST)
Rare Diseases and Orphan Drugs

Dongmin Xu

Trabectedin (Yondelis®, Pharma Mar S.A.)
- Aka euteinascidin-743, Et-743.
- Approved in 2015 for treatment of advanced soft-tissue sarcoma and ovarian cancer
- First isolation from sea squirt *Ecteinascidia turbinata* by Kenneth L. Rinehart in 1984
  - Samples collected on reefs in the West Indies by scuba diving
  - Preliminary assay showed promising anti-cancer activities
- Pharma Mar licensed Et-743 from University of Illinois in 1984 and started clinical trials
- Sea squirt farming is extremely inefficient; 1 g of Et-743 from 1 ton of sea squirts
- Rinehart asked E. J. Corey to devise a synthetic route for Et-743
  - This task was given to David Y. Gin, a postdoc in the Corey lab at that time
  - After postdoc, Gin joined the UIUC chemistry faculty and later relocated to Sloan-Kettering before tragically passing away at 43

Corey’s Total Synthesis of Et-743:

1) **Pd(PPh₃)₄**, 84%
2) **DPPA**, BnOH, 93%
3) **DBU**, 70%
4) **BF₃·Et₂O**, 73%
5) **Et₂O**
6) **Pd/C**, **H₂**
7) **AcOH**, **KCN**, 61%
8) **([R,R]-DiPAMP)+BF₄⁻**, 97%, 96% ee
9) **([R,R]-DiPAMP)**

(R, R)-DiPAMP

**Syntheses of Et-743, con’d:**

Fukuyama (2002): Ugi four-component reaction

\[
\begin{align*}
\text{Me} & \quad \text{OMOM} & \quad \text{NH}_2 & \quad \text{OTBS} \\
\text{Me} & \quad \text{BnO} & \quad \text{Me} & \quad \text{OMe} \\
\text{BocHN} & \quad \text{CO}_2\text{H} & & \\
\text{Me} & \quad \text{OMe} & & \\
\text{Me} & \quad & \quad & \quad + \\
\text{Me} & \quad \text{NN} & \quad \text{PMP} \\
\text{HN} & \quad \text{Boc} & \quad \text{Me} & \quad \text{OMe} \\
\text{BnO} & \quad \text{Me} & \quad \text{I} & \quad \text{CO}_2\text{H} \\
\text{TBSO} & \quad & \quad & \quad \\
90\% & \quad & \quad & \quad \\
\end{align*}
\]

\[\rightarrow \text{Et-743}\]

Semisynthesis (used by Pharma Mar for actual production):

\[
\begin{align*}
\text{Me} & \quad \text{OMe} & \quad \text{HO} & \quad \text{Me} \\
\text{MeO} & \quad \text{N} & \quad \text{Me} & \quad \text{H} \\
\text{NH} & \quad \text{CN} & \quad \text{OMe} & \quad \text{HO} \\
\text{Me} & \quad & \quad & \quad + \\
\text{Me} & \quad \text{HN} & \quad \text{O} & \quad \text{PMP} \\
\text{Me} & \quad \text{OMe} & \quad \text{OBn} & \quad \text{I} \\
\text{TBSO} & \quad & \quad & \quad \\
& \quad & \quad & \quad \\
21\% & \quad & \quad & \quad \\
\end{align*}
\]

\[\rightarrow \text{Et-743}\]

- 21 steps
- 1% overall yield

**Other syntheses:**

- Danishesky: *ACIE* 2006, 1754.
- Fukuyama: *JACS* 2013, 13684.
- Ma: *ACIE* 2019, 3972.

**Future outlook:**

- Changes in OD policy needed?
  - Shorter period of market exclusivity
  - Non-permanent orphan status
- Extension of orphan drug acts to other neglected diseases (e.g. tropical diseases)
- Problem: Most neglected diseases prevail in under-developed countries and regions
- A potential source for the next pandemic?

**Analogs:**

- Cyanosafracin B can be obtained via fermentation of the bacteria *Pseudomonas fluorescens*
- Late-stage sequence similar to Corey’s work

**Org. Lett. 2000, 2545.**

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**Org. Lett. 2000, 2545.**
Appendix: List of all FDA approved orphan drugs during 2020:

- Avapritinib (Ayvakit®, Blueprint Medicines)
  - GIST with PDGFRA exon 18 mutations
- Tazemetostat (Tazverik®, Epizyme)
  - Thyroid eye disease
- Tucatinib (Tukysa®, Seagen)
  - HER2-positive breast cancer
- Capmatinib (Tabrecta®, Norvatis)
  - NSCLC
- Osilodrostat (Isturisa®, Recordati Rare Diseases)
  - Cushing disease
- Selumetinib (Koselugo®, AstraZeneca)
  - Neurofibromatosis Type 1
- Pemigatinib (Pemazyre®, Incyte)
  - Cholangiocarcinoma
- Ripretinib (Qinlock®, Deciphera)
  - GIST
- Nifurtimox (Lampit®, Bayer)
  - Chagas disease
- Risdiplam (Evrysdi®, Genentech)
  - Spinal muscular atrophy
- Triheptanoin (Dojolvi®, Ultragenyx)
  - LC-FAODs
- Artesunate (Artesunate®, Amivas)
  - Severe malaria

Rare Diseases and Orphan Drugs

Non small-molecule drugs:
- Teprotumumab (Tepezza®, Horizon Therapeutics)
- Isatuximab (Sarclisa®, Sanofi)
- Inebilizumab (Uplinza®, Viela Bio)
- Tafasitamab (Monjuvi®, MorphoSys)
- Belantamab mafodotin (Blenrep®, GlaxoSmithKline)
- Viltolarsen (Viltepso®, Nippon Shinyaku)
- Satralizumab (Ensprynng®, Roche)
- Atoltivimab/odesivimab/mattivimab (Inmazeb®, Regeneron)
- Lumasiran (Oxlumo®, Alnylam)
- Naxitamab (Danyelza®, Y-mAbs Therapeutics)
- Ansvimab (Ebanga®, Ridgeback)

Selpercatinib (Retevmo®, Eli Lilly)
- RET-positive NSCLC

Lurbinectedin (Zepzelca®, Pharma Mar S.A.)
- SCLC

Copper dotatate Cu-64 (Radiomedix)
- Imaging & cancer treatment

Lonafarnib (Zokinvy®, Eiger Biopharma)
- HGPS

Decitabine/cerazuridine (Inqovi®, Otsuka)
- Myelodysplastic syndromes

Berotralstat (Orladeyo®, BioCryst)
- Hereditary angioedema

Setmelanotide (Imcivree®, Rhythm)
- Rare genetic diseases of obesity

Pralsetinib (Gavreto®, Blueprint Medicines/Roche)
- RET fusion-positive NSCLC