Разработка препаратов для лечения БШМТ. Часть 2

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Подробнее о генетических тестах

Пошаговая стратегия

1. Проверить количество копий PMP22*

2. Проверить точечную мутацию* PMP22 + остальные 3 гена

3. Панель генов БШМТ

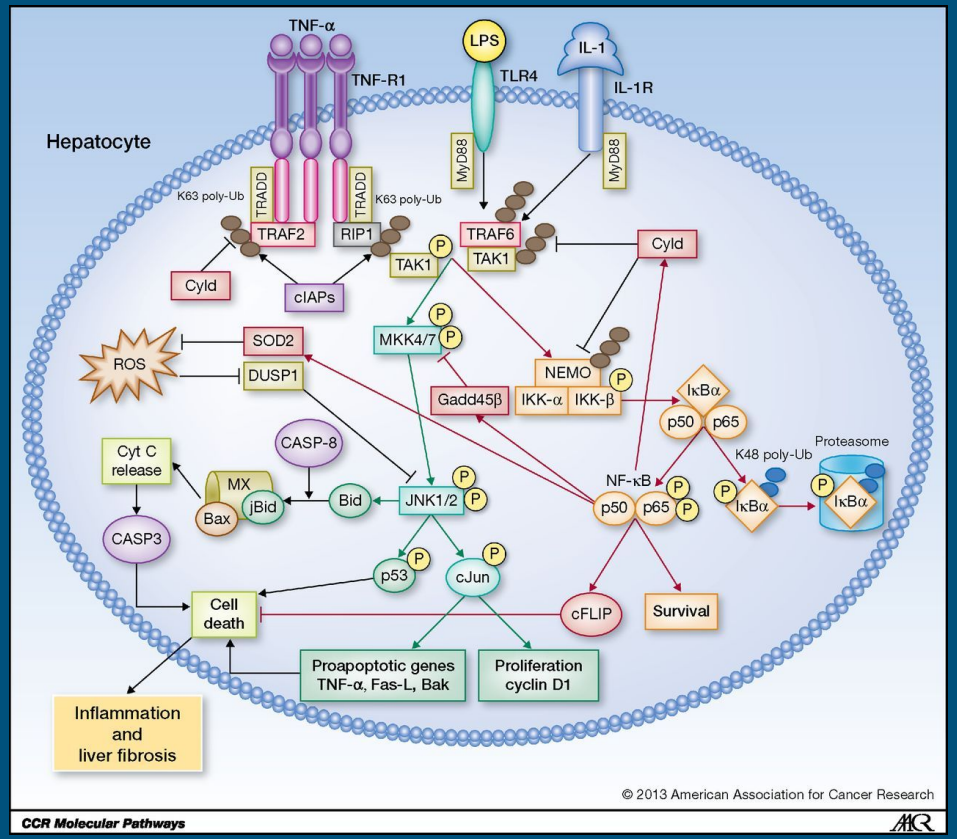
4. Экзом/геном

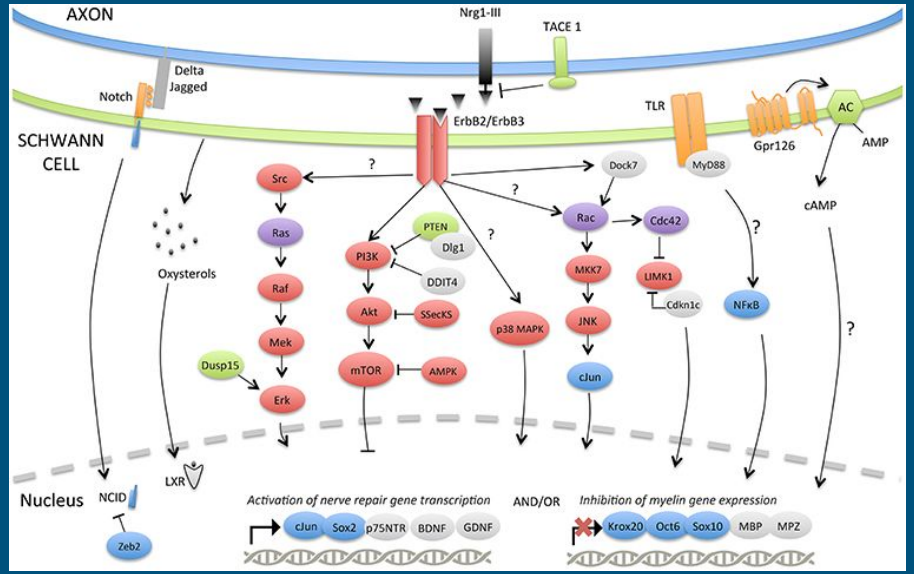
*ПЦР для определения кол-ва копий, секвенирование для точечных мутаций)

	Отдельные гены	Панель генов	Экзом, геном
Гены	**PMP22** (дупликация (тип 1A), точечная мутация (тип 1E)) **GJB1** (различные мутации, белок миелина conexin-32 (тип CMT1X)) **MPZ** (peripheral myelin protein, различные мутации (тип 1B)) **MFN2 (**mitofusin 2, митохондриальный белок, точечные мутации, (тип 2, в основном A))	- Общая панель - Аксональный тип - Демиелини-зирующий тип	Экзом - только та часть генома (ДНК), которая кодирует белки (функциональные единицы) Геном - все последовательности ДНК
Лаборатории	Хеликс (определение числа копий PMP22 - 2700 р) и ЛМД (3000 р) Genotek (один ген - 24 990 р, нет поиска дупликация в PMP22) Геномед (дупликация PMP22 - 5000 р, поиск мутаций в PMP22 - 9000 р, поиск мутаций в гене GJB1 - 6500 р, поиск мутаций в гене MFN2 - 26000 р)	Genotek (все 3 панели 27990 р) Геномед (от 7000 до 12000 р в зависимости от гена/генов)	ДНКом (экзом - 65000 р) Genotek (экзом - 29990 р) Genetico (экзом от 46000 р, геном от 139000 р) Геномед (экзос от 43000 р, геном от 99000 р) Atlas (полный геном - 89500 р)

Обзор некоторых компаний, предоставляющих генетические тесты в России - https://vc.ru/life/32760-gid-po-geneticheskim-testam-v-rossii-kakoy-vybrat-i-gde-zakazat

Молекулярные пути сложны и запутаны



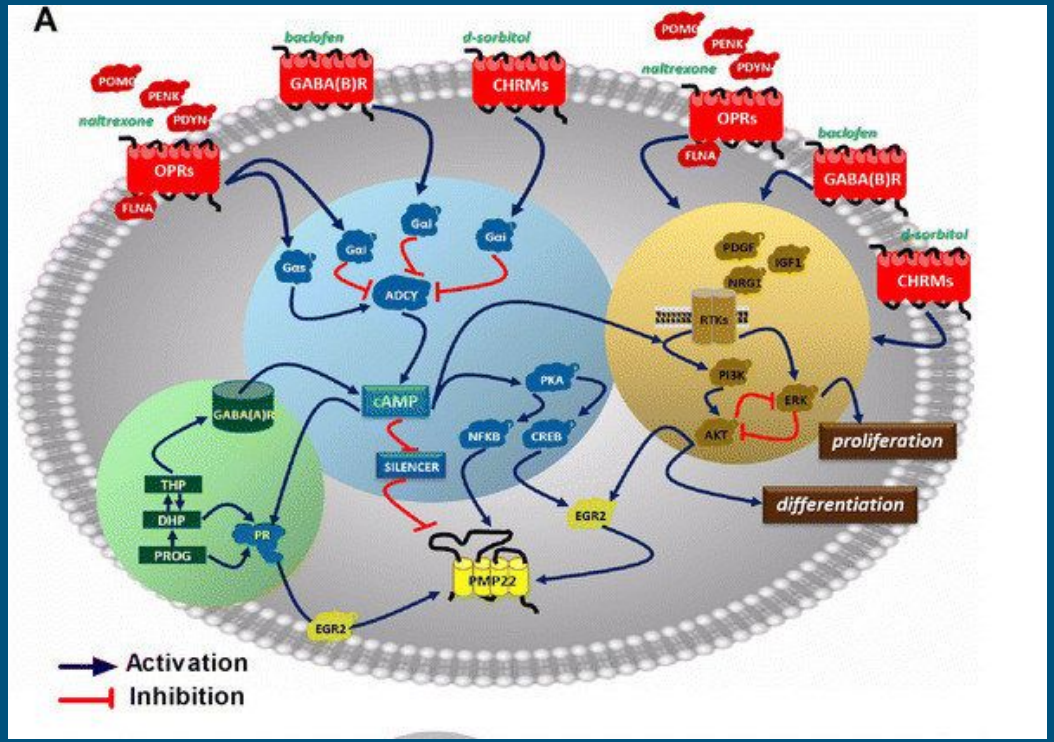


https://clincancerres.aacrjournals.org/content/19/11/2810.figures-only

https://www.frontiersin.org/articles/10.3389/fnmol.2017.00038/full

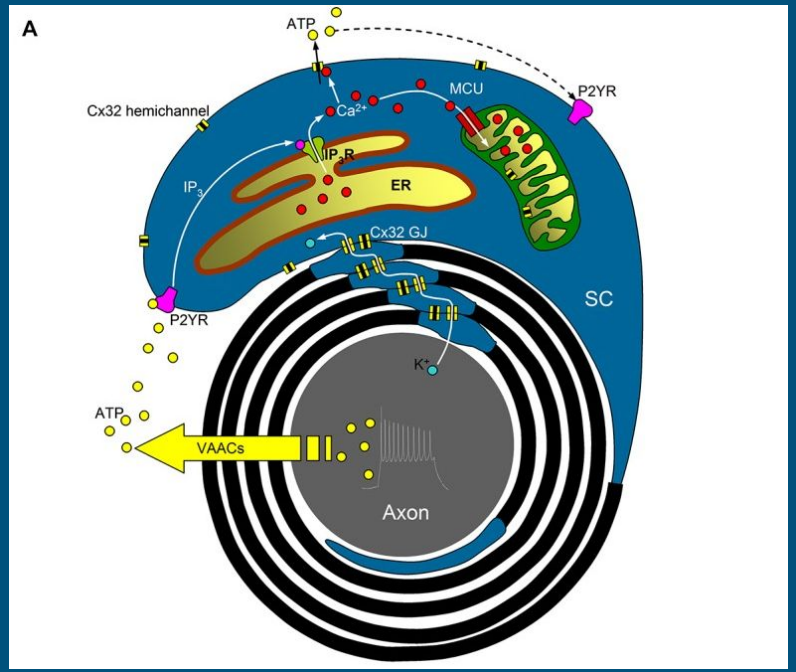
Всё зависит от типа!

Разная причина (разные поломки разных генов, разные молекулярные пути) - разное лечение



Пути, регулирующие экспрессию PMP22

https://www.researchgate.net/publication/269466399_Polytherapy_with_a_combination_of_three_repurposed_drugs_PXT3003_down-regulates_Pmp22_over-expression_and_improves_myelination_axonal_and_functional_parameters_in_models_of_CMT1A_neuropathy



Предполагаемые функции connexin-32 (кодируется геном **GJB1**)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6048289/

Разработка лекарств

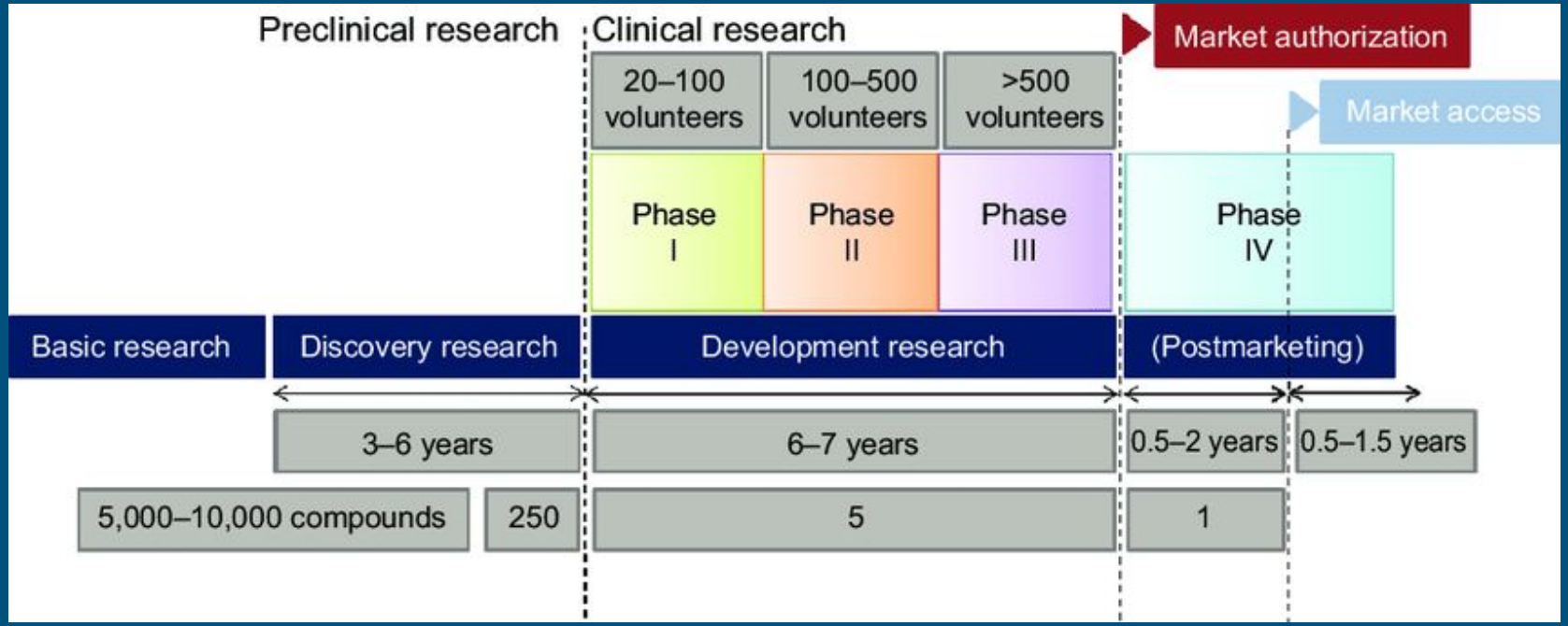
- Дорого (мил-трил $)
- Долго (>10 лет)
- Рискованно (одобряется ~1 из 10 препаратов, дошедших до фазы I)
- Невыгодно (для орфанных заболеваний)

Идентификация кандидатов
Культуры клеток

Доклиника:
Животные

Клиника: люди

Фаза I Фаза II Фаза III Фаза IV

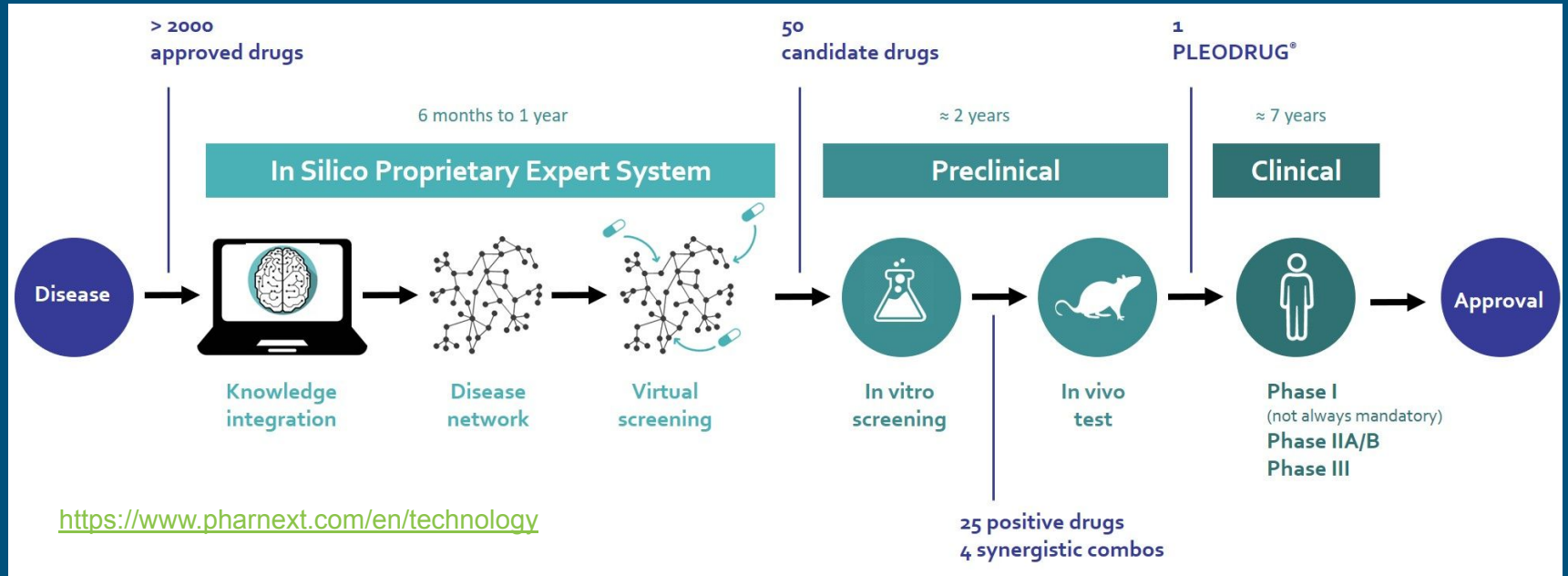


https://www.researchgate.net/publication/268787481_The_role_of_health_technology_assessment_bodies_in_shaping_drug_development
https://www.raps.org/regulatory-focus/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fdas-priority-review-vouchers

Pharnext: подход компании

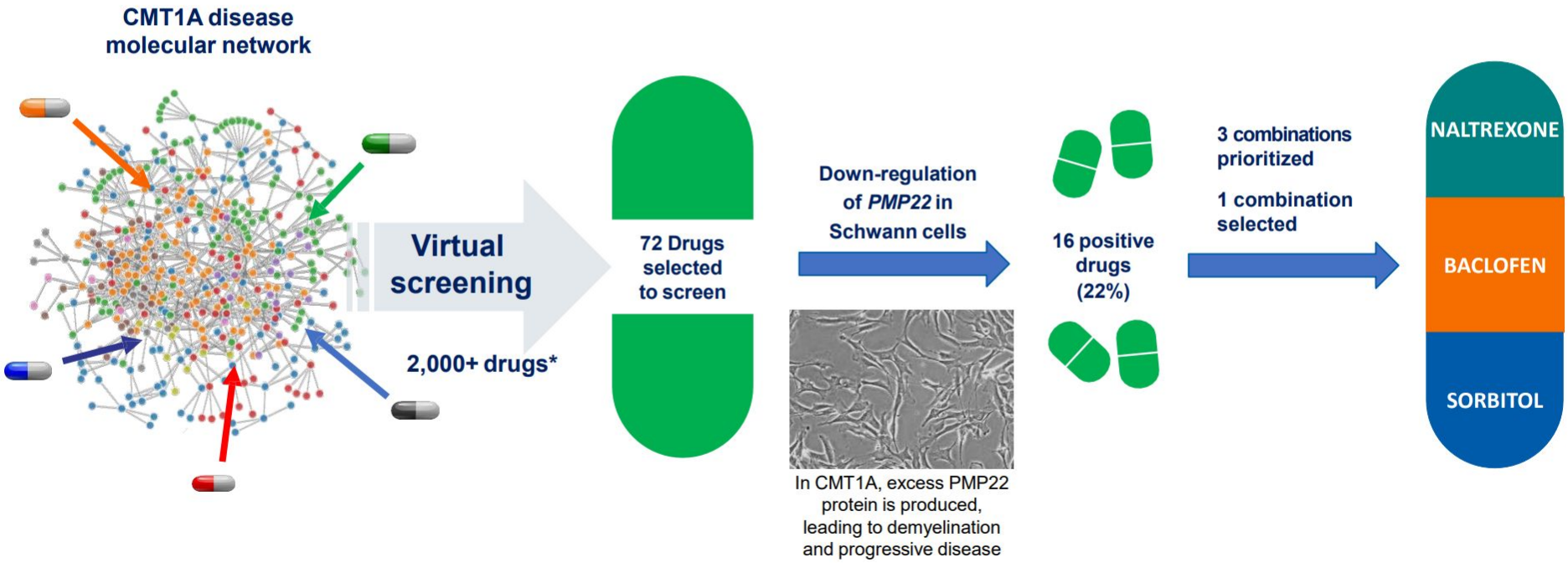
Новые терапевтические подходы для нейродегенеративных заболеваний (БШМТ тип 1а, болезнь Альцгеймера)

1. Анализ молекулярных путей, нарушенных при заболевании
2. Подбор комбинаций уже одобренных препаратов для воздействие на обнаруженные из 1 молекулярные пути



https://www.pharnext.com/en/technology

Discovery of PXT3003 for CMT1A
Led to Positive Phase II and Promising Phase III Data



https://www.pharnext.com/en/investors/presentation

* All currently approved for marketing by FDA.

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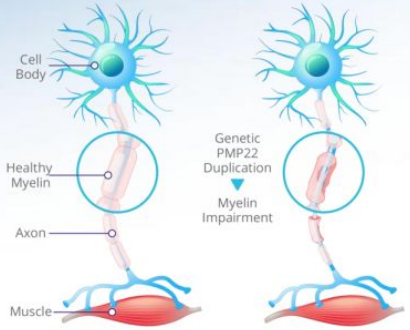
Подход: анализ путей PMP22 и способов воздействия на них

PXT3003 Novel Design and Mechanism of Action

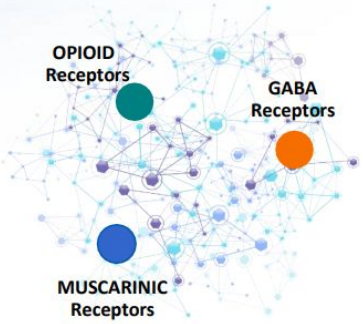
CMT1A disease at-a-glance



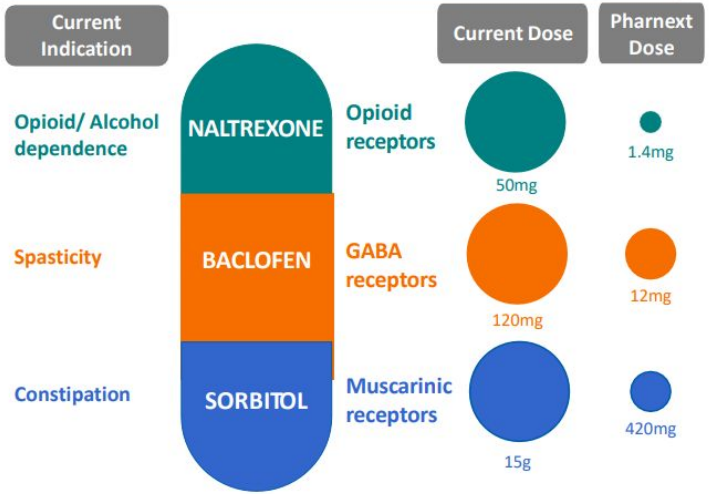
Normal

CMT1A - Axonal dysfunction and muscle loss

Network analysis



Design of PXT3003



https://www.pharnext.com/en/investors/presentation

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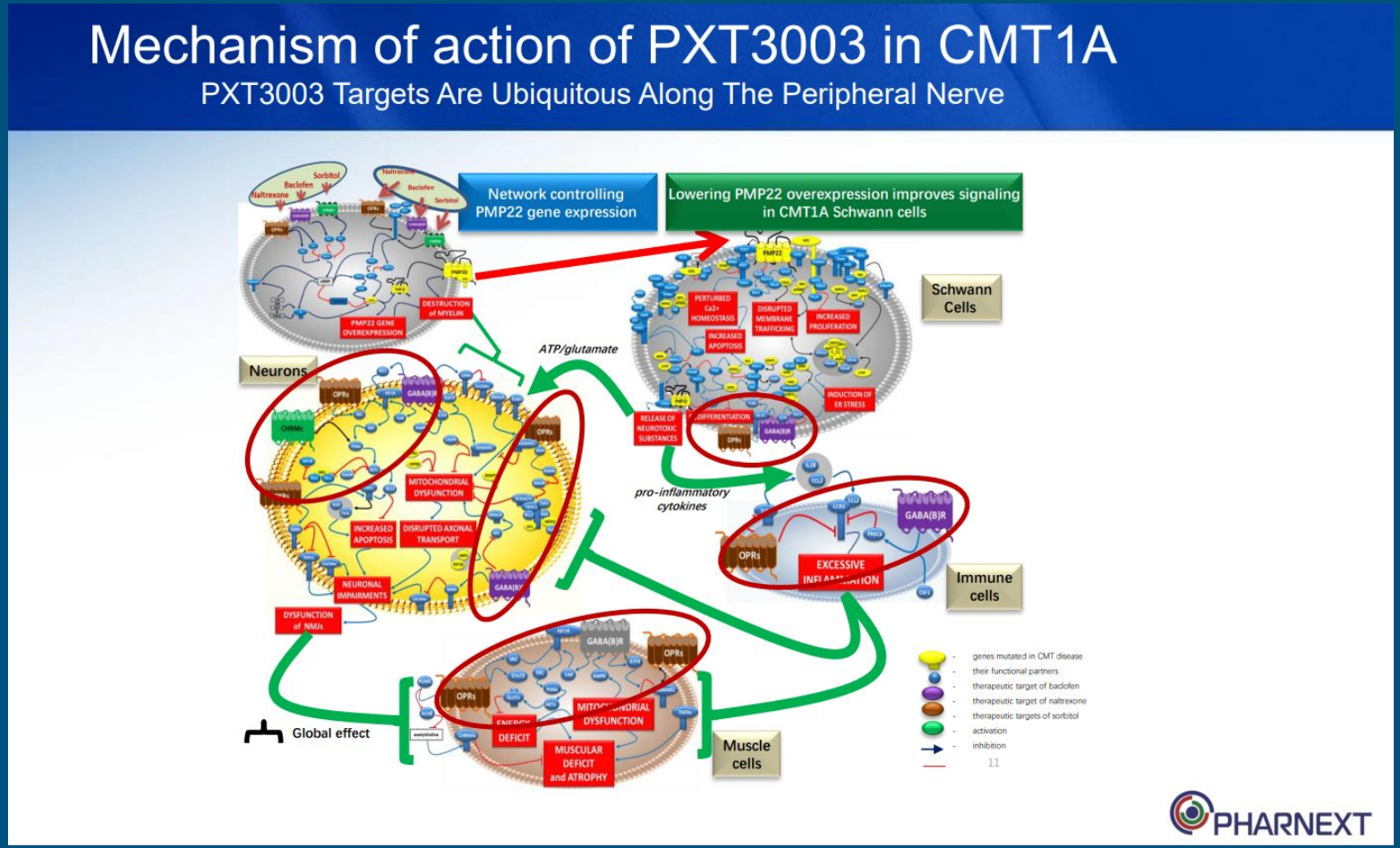
Подойдет ли PXT3003 для лечения других типов ШМТ? Скорее всего, нет.



И может быть опасным:

новая мутация, вызывающая ШМТ, в гене SORD (дегидрогеназа сорбита) - повышенный уровень сорбита

PXT3003 модулирует опиоидные, ГАМК и мускариновые рецепторы, снижая экспрессию PMP22

Почему нужно ждать еще дольше?

CMC Overview

De-risking our Dose Format for Second Phase III Study

- 10mL of low dose = 5mL of high dose
- For the second Phase III study, we are delivering the high dose by dosing patients with 10mL of the low dose concentration, since the low dose concentration does not have the issue with crystals
- This same approach was used for the prior Phase III extension study with the approval of regulatory agencies
- We are also planning to use unit dose “stick packs” for better convenience and compliance

Why?

- High dose solution in 100mL bottles exhibited a small amount of crystal precipitate (~ 2% by volume) in some batches due to a reaction between baclofen and paraben

Future

- In parallel, we are developing both a room temperature oral solution as well as a solid oral dosage form which will better serve patients on a commercial basis

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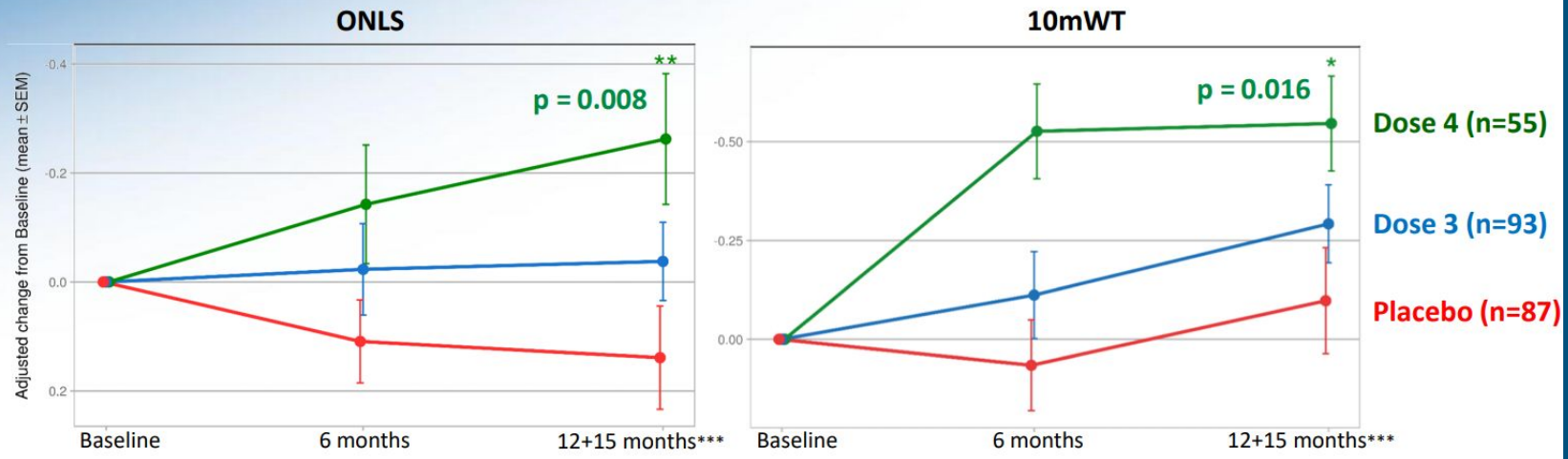
Как долго принимать: постоянно. Кому: БШМТ тип 1а 15-65 лет, средней тяжести

PLEO-CMT: ONLS and 10MWT in SAP Primary Population



*, ** Dose 4 vs Placebo, ANCOVA with multiple imputation (Missing data implemented by multiple imputations following the placebo trend)

*** Average of 12 and 15 Month, or 12 Month if 15 Month is missing

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Сколько еще ждать?

Other PXT3003 Milestones and Anticipated Path Forward

Feb 2, 2019: FDA Fast Track Designation granted

Jan 6, 2020: Announced top-line results of extension study (PLEO-CMT-FU) of long-term safety and efficacy of PXT3003

April 23, 2020: Received clarity on second Phase III trial protocol in CMT1A from FDA

3Q 2020: Submit Special Protocol Assessment (SPA) to FDA

1Q 2021: Expect to Initiate second Phase III trial (FPFD) in CMT1A

Continual assessment of commercial partnership options for various geographies, including US, EU, Japan and ROW; China commercialization rights are licensed to GeneNet, a JV formed by Pharnext & Tasly

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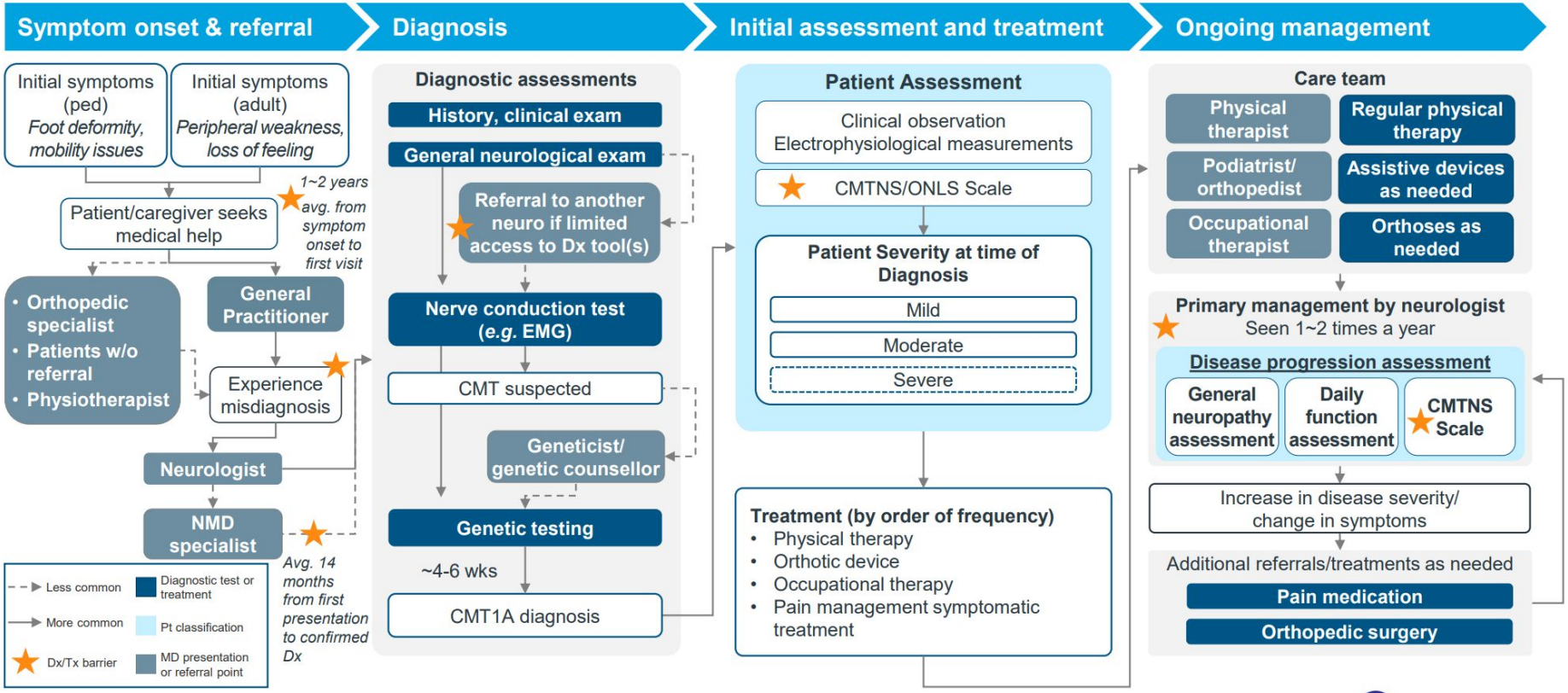
Overview of CMT1A Patients Journey



 Source: Market research study conducted in the US and EU5 in 2019 with IQVIA

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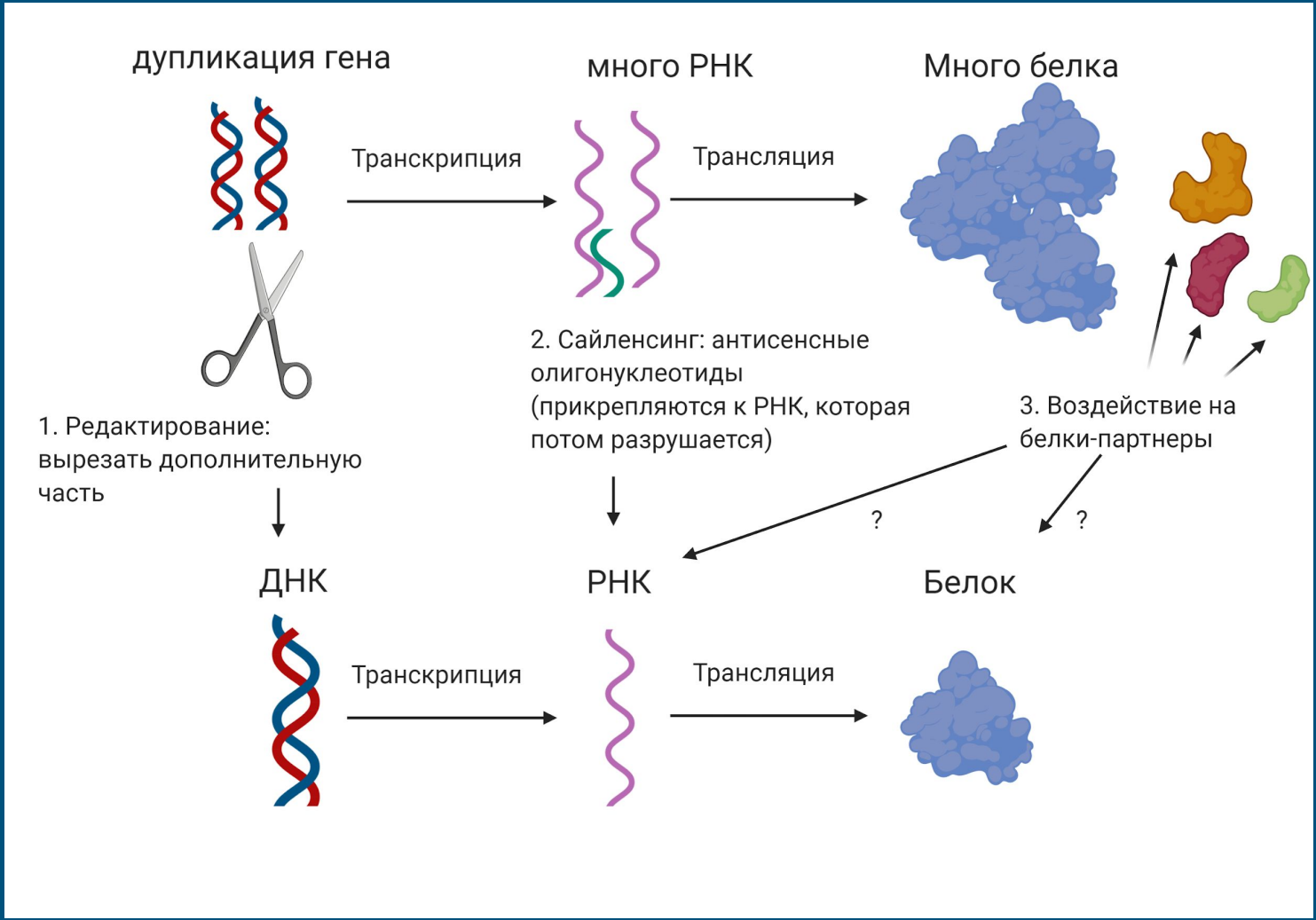
Компании, разрабатывающие лекарства для БШМТ (в сотрудничестве с cmtausa.org) - программа STAR

STAR: The Webinar - https://www.youtube.com/watch?v=qHRjI7H0wgA&list=PL7CuX3ETmTf1C9T9L0sWCvl0oesZmWyG7&index=9&t=0s
Список партнеров: https://www.cmtausa.org/our-research/for-researchers/strategic-partners/

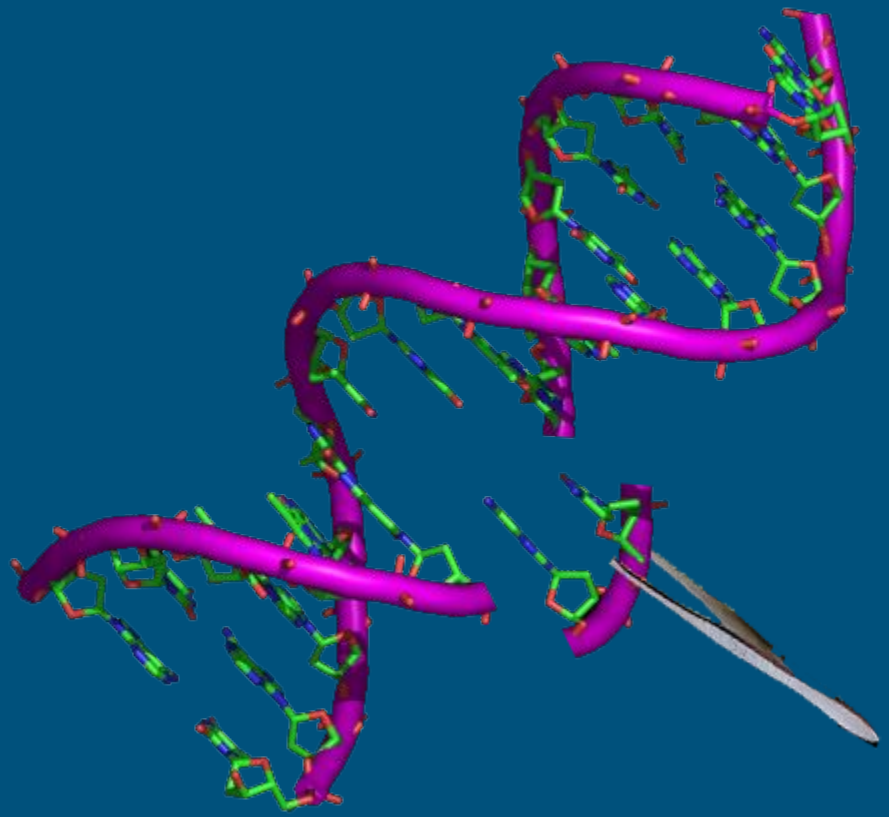
Подходы для лечения типа 1а (дупликация гена PMP22)



Подходы в разработке лекарств для разных типов

Генетическая терапия, которая зависит от гена и типа мутации

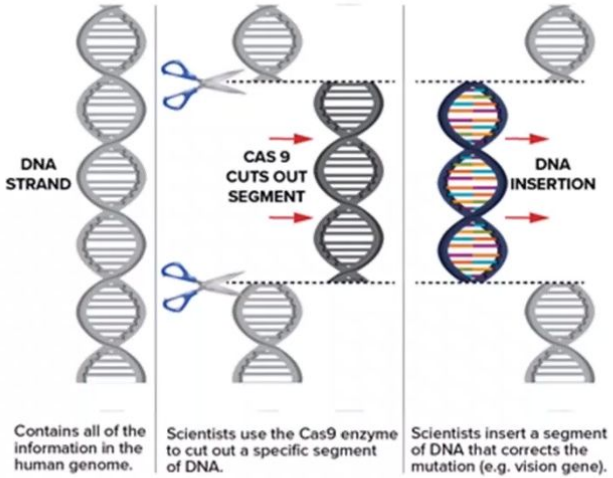
- редактирование генов (CRISPR)
- замена на здоровый ген (при наличии мутации или отсутствии гена)
- сайленсинг (выключение) генов



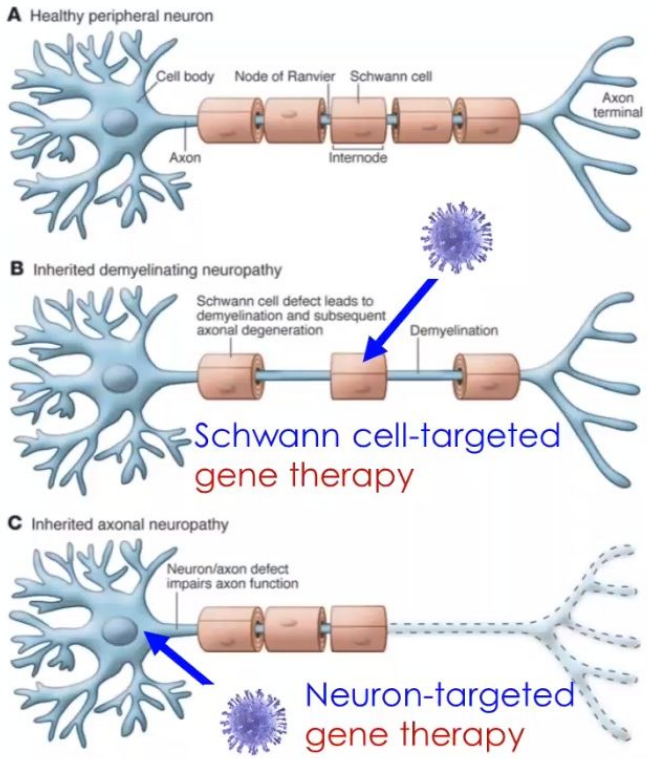
CMTA
Charcot-Marie-Tooth Association

What is Gene Therapy?

- **Gene Therapy is the use of genes or gene editing as treatment**
- Involves introduction of genetic material (DNA or RNA) in the cells and tissues of an individual instead of drugs or surgery
- **Several gene therapy approaches include:**
  1. **Replacing** a faulty (missing or mutated) gene that causes a disease with a healthy copy of the gene
  2. **Inactivating or 'silencing'** a mutated gene that is functioning improperly (has toxic gain of function effects)
  3. **Editing** part of a mutated toxic gene through "cut and paste" approach



What are the Potential Gene Therapies?



Gene therapies have to address the disease mechanism:

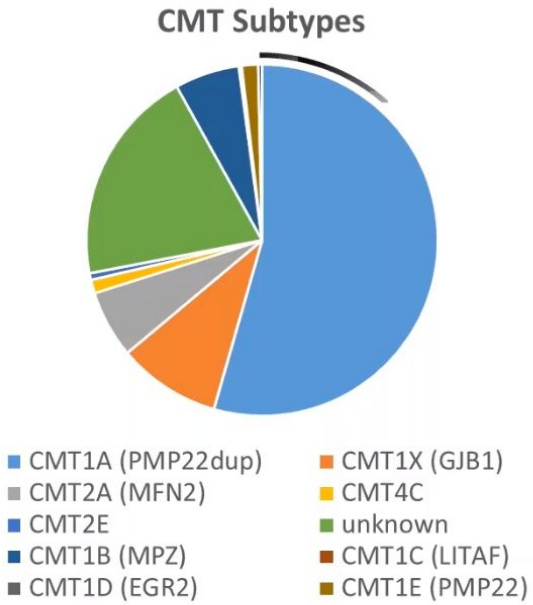
- For CMT neuropathies caused by loss of function (mostly CMT 4 and X) mechanisms we can deliver the healthy gene to restore the function (gene replacement)
- For CMT neuropathies with toxic gain of function (mostly CMT 1 and 2) mechanism we can either silence (reduce) the toxic gene or try to repair (edit) the mutation

In most cases **gene therapies have to be delivered to the affected cell type**:

- Therapies for demyelinating CMT have to be targeted to Schwann cells
- Therapies for axonal CMT neuropathies need to be delivered to neurons and their axons

Comprehensive Gene Therapy Efforts

1. The CMTA sponsors gene therapy development for many types of CMT:
   a) CMT1A
   b) CMT1X
   c) CMT4C
   d) CMT2A
   e) Others in development
2. Many technologies
   a) AAV Delivery
   b) Gene Silencing
   c) Gene Replacement
   d) Genome Editing: CRISPR-Cas9
   e) Antisense Oligonucleotides (ASO)



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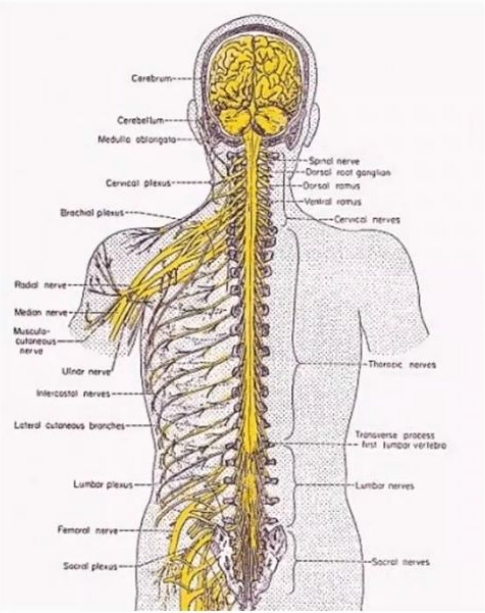
Genome Editing: CRISPR-Cas9

Genome Editing: Using CRISPR-Cas9 to fix the causative mutation or remove the mutation:

- Motor Neuron Disease:
  Partnering with a leading genome editing group: CMT2A, CMT2E, CMT2F

- CMT1A (in this case to reduce levels):
  Toolgen



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Current Activities to Prepare for Trials

1. Evaluation of different vectors for targeting Schwann cells
2. Evaluation of different delivery routes
3. Evaluation of possible toxicity
4. Evaluation of bio-distribution
5. Provide the proof-of principle for treating all CMT1X mutations
6. Test treatment before and after the onset of the neuropathy in CMT1X
7. Test AAV-mediated gene replacement in CMT4C model

Relevant for all CMT types 1 and 4

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STAR Gene Therapy: the Future is Now

	Gene Replacement AAV	Gene Silencing ASO, RNAi	Gene Editing CRISPR-Cas9
Loss of Gene Function	1X = Kleopa 4C = Kleopa		
Alteration of Gene Function	2A = Passage Bio 2E under review	1A = Ionis Kleopa/Gray/Svaren 2D = Nationwide	2A + 2E + 2F = UCSF 1A = Toolgen

Delivery to Neurons: approved for SMA (ASOs, AAVs)

Delivery to Schwan Cells = Kleopa/Gray/Svaren

Biomarkers

Терапии для ШМТ на данный момент

	STAR BIOTECH & ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT PIPELINE STAGE					
			Discovery	Research Tools	Preclinical	Phase1	Phase2	Phase3
1A	Pharnext	Small Molecule						P3
1A	Acceleron*	Biological					P2	
1A	InFlectis BioScience	Small Molecule				P1/P2		
1A	Cyprus + University of Wisconsin + University of Texas, SW	Gene Therapy			Preclinical			
1A	Ionis	Gene Therapy			Preclinical			
1A	National Institutes of Health*	Assays/Small Molecule			Preclinical			
1A	Regenacy Pharmaceuticals	Small Molecule			Preclinical			
1A	Sanofi*	Small Molecule/Biomarkers			Preclinical			
1A	Star Biotech Partner A	Small Molecule			Preclinical			
1A	Star Biotech Partner B*	Small Molecule			Preclinical			
1A	Star Biotech Partner C	Gene Therapy			Preclinical			
1A	Star Biotech Partner D	Biological			Preclinical			
1A	University of Rochester, NY	Biomarkers (Wearables)			Preclinical			
1A	University of Wisconsin + Memorial Sloan Kettering	Target Discovery	Discovery					
1B	Acceleron*	Biological					P2	
1B	InFlectis BioScience	Small Molecule				P1/P2		
1B	National Institutes of Health*	Assays/Small Molecule			Preclinical			
1B	San Raffaele Scientific Institute	Small Molecule			Preclinical			
1B	Universities of Iowa and Wisconsin	Biomarkers			Preclinical			
1B	University of Iowa	Target Validation			Preclinical			
1B	University at Buffalo, NY	Animal Model/Target Validation		Laboratory				
1B	University at Buffalo, NY	Target Discovery	Discovery					
1X	Acceleron*	Biological					P2	
1X	Cyprus Institute	Gene Therapy			Preclinical			
1X	University of Pennsylvania	Target Validation			Preclinical			
1X	University of Illinois (Chicago)	Animal Model		Laboratory				
1X	The Jackson Laboratory	Animal Model		Laboratory				
2A	Passage Bio + University of Pennsylvania	Gene Therapy			Preclinical			
2A	Regenacy Pharmaceuticals	Small Molecule			Preclinical			
2A	Star Biotech Partner E	Small Molecule			Preclinical			
2A	Star Biotech Partner A	Small Molecule			Preclinical			
2A	Star Biotech Partner F	Peptide			Preclinical			
2A	University of Iowa	Respiratory Study					P2	
2A	University of Pennsylvania	Animal Models		Laboratory				
2A	Star Partner G	Small Molecule	Discovery					
2A	Gladstone Institute (University of California, San Francisco)	Gene Therapy (CRISPR)	Discovery					
2A	Washington University	Small Molecule	Research Interest					
2E	Regenacy Pharmaceuticals	Small Molecule			Preclinical			
2E	STAR Biotech Partner D	Biological			Preclinical			
2E	Nationwide Children's Hospital + Ohio State University	Gene Therapy			Preclinical			
2E	Columbia University	Small Molecule			Preclinical			
2E	University of Miami	Small Molecule			Preclinical			
2E	Gladstone Institute (University of California, San Francisco)	Gene Therapy (CRISPR)			Preclinical			
2E	Columbia University	Animal Model		Laboratory				
4	4C - Cyprus Institute	Gene Therapy			Preclinical			
4	4J - Neurogene	Gene Therapy			Preclinical			
ALL TYPES	Psychogenics + Cleveland Clinic + Charles River	Preclinical Testing Partners			Preclinical			
ALL TYPES	Inherited Neuropathies Consortium	Research & Clinical Tools			Preclinical			
ALL TYPES	New York Stem Cell Foundation	Stem Cell Lines		Laboratory				
ALL TYPES	University of Miami	Gene Identification	Discovery					
ALL TYPES	Jackson Laboratories	Animal Models		Laboratory				

*Project Concluded

Полезные источники на английском

Charcot-Marie-Tooth Association (CMTA) - https://www.cmtausa.org/
Hereditary Neuropathy Foundation - https://www.hnf-cure.org/donate-cmt-research/
вся полезная информация по ШМТ
ШМТ новости - https://charcot-marie-toothnews.com/

ClinicalTrials.gov - https://clinicaltrials.gov/ct2/home
База клинических исследований

Biomindmap - https://biomindmap.com/
База биологических и медицинских данных

Pharnext - https://www.pharnext.com/en/
Компания-производитель PXT3003

Google Scholar https://scholar.google.com/ и Pubmed https://pubmed.ncbi.nlm.nih.gov/ для поиска исследований

Отблагодарить Ларису:
PayPal: kito00san@gmail.com
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4100115765990270

Отправить деньги на исследования:
https://interland3.donorperfect.net/weblink/weblink.aspx?name=E13111&id=112&_ga=2.81225438.81481407.1599195318-1569679455.1575433477