Moderna's therapeutics: Relaxin (mRNA-0184)

Last program update: November 4, 2021

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	**mRNA-0184**						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	mRNA-4157						50-50 global profit sharing with **Merck**
	KRAS vaccine	mRNA-5671						50-50 global profit sharing with **Merck**
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
	IL-12 *Solid tumors*	MEDI1191						50-50 U.S. profit sharing; **AZ** to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	AZD8601						**AZ** to pay milestones and royalties
	Propionic acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic acidemia (MMA)	mRNA-3705						Worldwide
Systemic Intracellular Therapeutics	Glycogen storage disease type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar syndrome type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge
Inhaled Pulmonary Therapeutics	Cystic fibrosis (CF)	VXc-522						**Vertex** to pay milestones and royalties

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Relaxin is a naturally occurring hormone

Human relaxin-2 is a **naturally occurring hormone**, present in both men and women, that becomes elevated in pregnant women

It is a vasoactive peptide **associated with cardiovascular remodeling** – protects from vascular overwork, increases renal function, promotes cell growth and survival and maintains vessel structure

Subsequent studies have **implicated relaxin's role beyond pregnancy**, through vasodilatory, antifibrotic, anti-inflammatory and protective effects on multiple organs

Tietjens J, Teerlink JR. Serelaxin and acute heart failure. Heart. 2016 Jan;102(2):95-9
Adapted from Du et al. *Nat Rev Cardiol.* 2010;7:48-58

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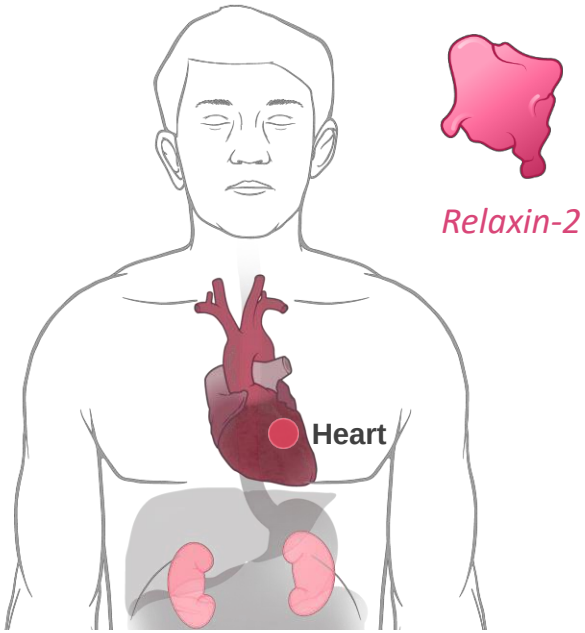
Evidence suggests relaxin has impact on cardiovascular disease



Relaxin-2

- **Relaxin activates a variety of pathways**, contributing to the reduction of oxidative stress, fibrosis, and inflammation
- Large body of evidence exists to support relaxin's clinical potential in several therapeutic areas, with its **impact on cardiovascular disease having been studied in both preclinical and clinical settings**

↓ Myocardial overload

↑ Renal function

↑ Cell preservation

↑ Extracellular matrix (ECM) remodeling

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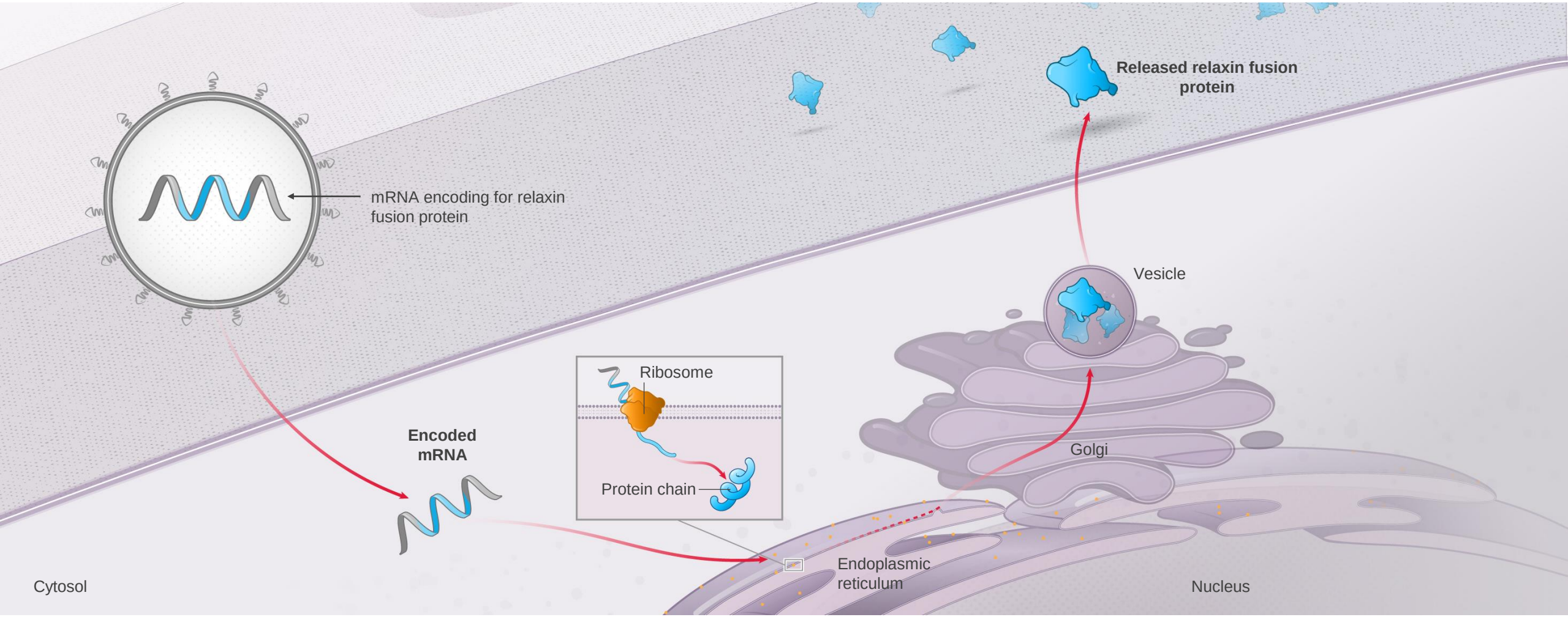
Relaxin therapy (mRNA-0184) encodes for relaxin fusion protein



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Moderna's relaxin program (mRNA-0184) is being developed to treat decompensated heart failure

- Acute heart failure (AHF) is defined as the new onset or worsening of symptoms and signs of heart failure (HF)
- In developed countries, HF has become a substantial public health problem, affecting 2% of the adult population
- AHF is the most frequent cause of unplanned hospital admission in patients of >65 years of age
- **Period after discharge is known as 'vulnerable phase' (2-3 months):**
  - 25% of patients readmitted within 30 days[1]
  - 30-day mortality rate of 5-10%[2,3]
  - 3-month readmission rates are ~30%[4,5,6]
  - Mortality is estimated at 25 – 30% at 1 year

– HF decompensation contributes to often permanent further decline in disease

Heart Failure Symptoms Outcomes
▪ Dyspnea (shortness of breath)
▪ Fatigue
▪ Pulmonary rales (abnormal crackling sounds)
▪ Peripheral oedema
▪ Distended jugular veins

(1) https://www.nature.com/articles/nrcardio.2015.14 (2) https://jamanetwork.com/journals/jama/fullarticle/185996 (3) https://www.sciencedirect.com/science/article/pii/S073510971001908X?via%3Dihub
(4) https://www.sciencedirect.com/science/article/pii/S0735109714002915?via%3Dihub (5) https://onlinelibrary.wiley.com/doi/10.1002/ejhf.566 (6) https://onlinelibrary.wiley.com/doi/10.1002/ejhf.1020

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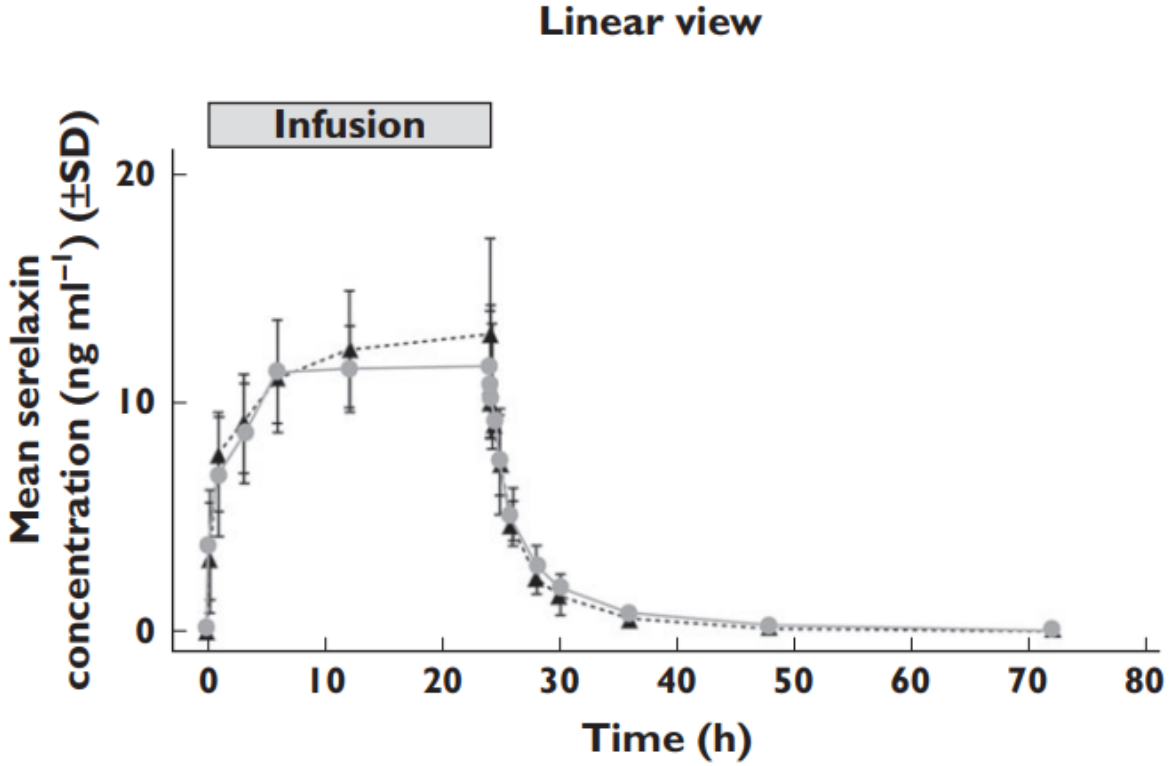
Longer duration relaxin and repeated infusions could allow for improved efficacy

Serelaxin (recombinant human relaxin-2) in a Phase 2/3 study

- Despite promising early results, the pivotal trial did not meet its primary endpoint

Recombinant relaxin-2

Serelaxin Serum Concentration – Time Profiles



Data shown as arithmetic mean with standard deviation in linear and semilogarithmic views for groups of patients with mild hepatic impairment compared with healthy controls

Kobalava, Zhanna et al. "Pharmacokinetics of serelaxin in patients with hepatic impairment: a single-dose, open-label, parallel group study," *BR J Clin Pharmacol,* (2015), https://doi.org/10.1111/bcp.12572

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Longer duration relaxin and repeated infusions could allow for improved efficacy

Serelaxin (recombinant human relaxin-2) in a Phase 2/3 study

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Moderna's technology and strategy may address these shortcomings through the following approaches:

- Long-acting form of relaxin has potential for extended disease impact
- Repeat acute/sub chronic dosing could extend the expected impact on cardiovascular disease (vs. single acute dosing with serelaxin)
- Indication strategy and trial design will prioritize an approach supporting clinical endpoints

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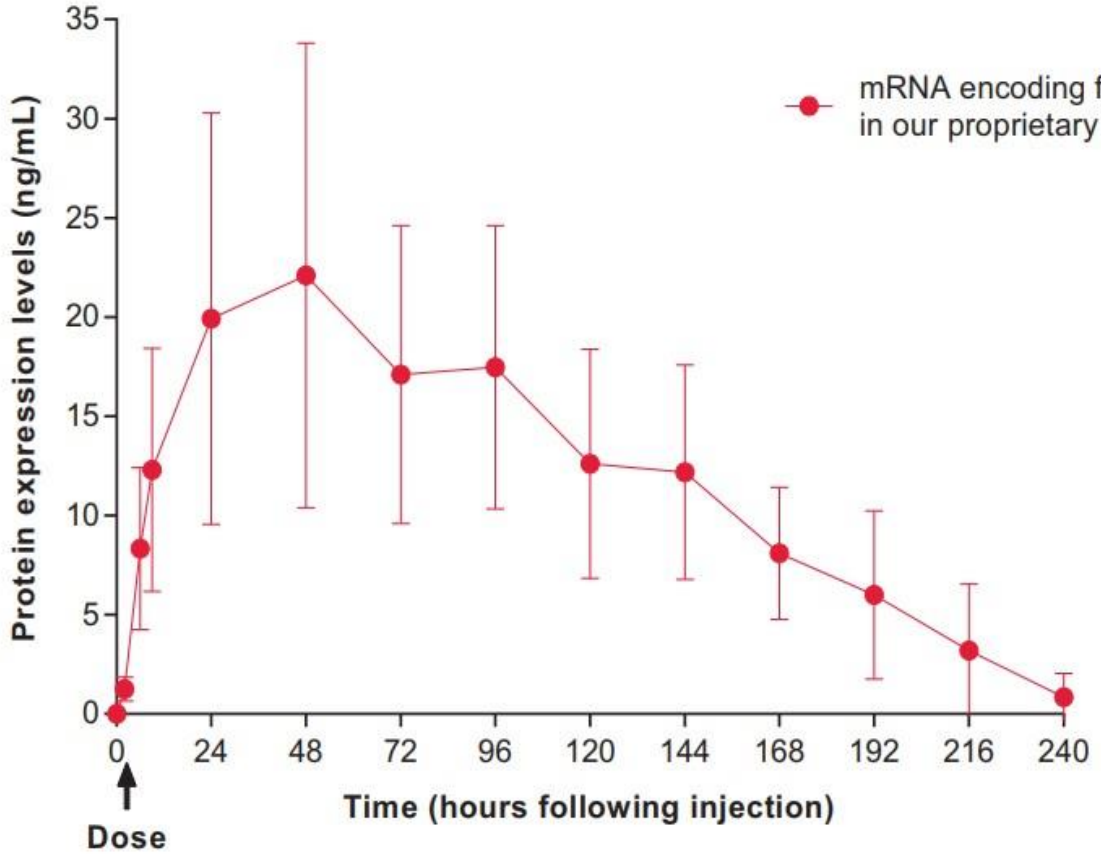
Previous relaxin collaboration saw protein expression in NHPs

- Preliminary protein expression data in non-human primates (NHPs) supports hypothesis of extended pharmacology relative to historical efforts with recombinant protein

- Advantages of mRNA delivery of relaxin fusion protein over earlier recombinant relaxin approaches:
  - Significantly increased half-life
  - No need for continuous IV infusion to maintain relaxin levels
  - Feasibility of repeat dosing

AZD7970: Protein expression up to 10 days in NHP



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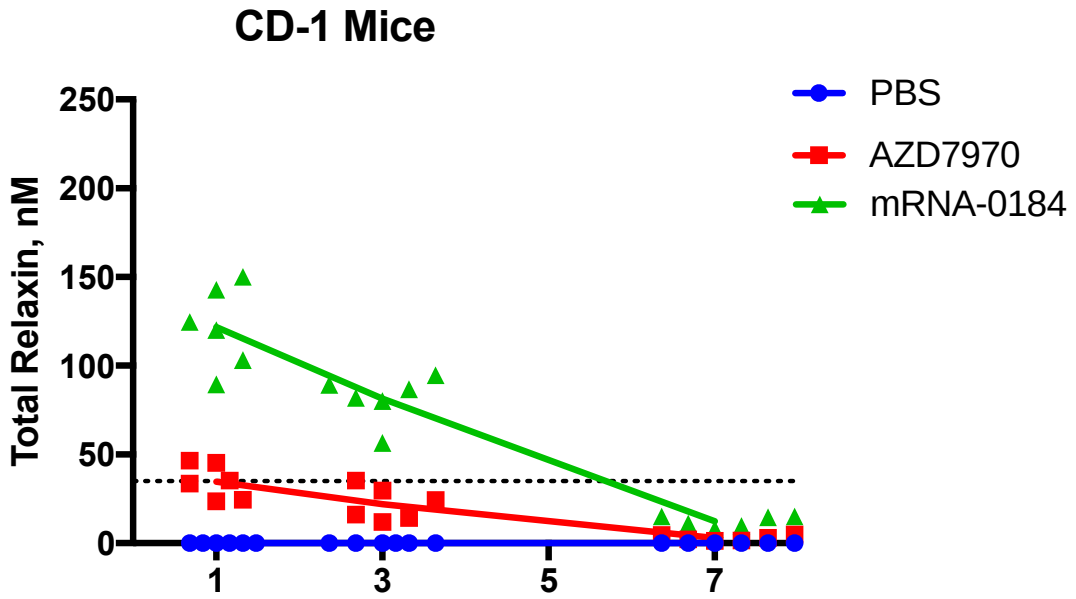
We are preparing to enter the clinic in chronic heart failure

Moderna's relaxin candidate (mRNA-0184)

- Introduction of a drug product with better pharmacology relative to AZD7970
- mRNA sequence engineered to increase protein expression and prolong half-life
- Additional NHP and preclinical studies ongoing
- Planning for a Phase 1 study in participants with chronic heart failure
  - Relaxin (mRNA-0184) to be administered after HF decompensation to bridge patients through the vulnerable period
  - Prior knowledge and use of biomarkers as clinical endpoints could help accelerate the overall development plan

Increase in expression observed in mice with mRNA-0184 vs. AZD7970 with sequence change



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