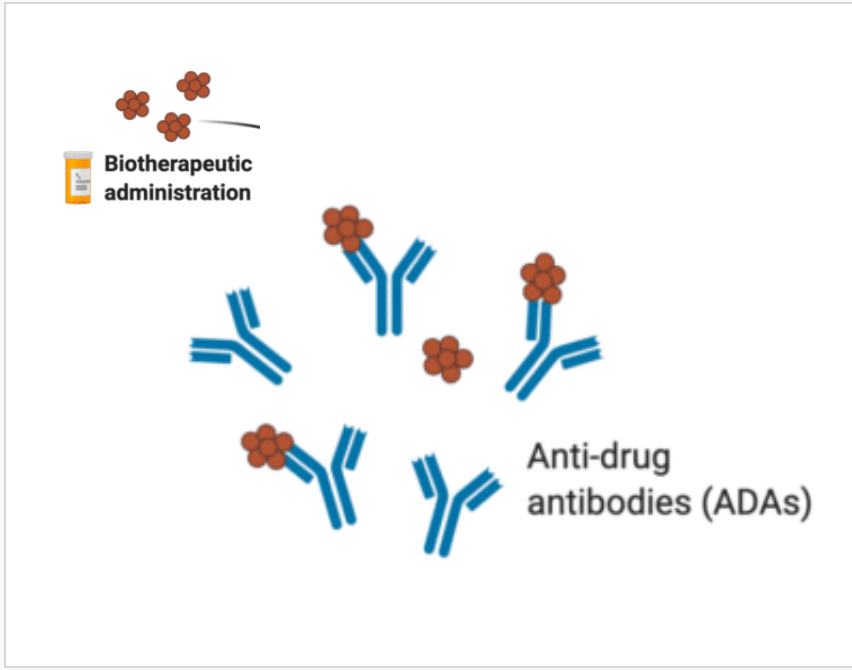
Anti-Drug Antibodies: A Major Barrier in Protein Therapeutics

Anti-drug antibodies (ADAs)

- Novel structures in a drug not seen during fetal development are usually immunogenic
- Drug immunogenicity manifests in the generation of ADAs

Negative Impacts of ADAs

- ADAs cause drug-resistance as they neutralize the drug's therapeutic effects
- ADAs can alter a drug's PK and PD properties, reducing drug efficacy
- Infusion reaction including anaphylaxis



AdaMunix

Regulator’s View

“

Immunogenicity studies primarily **focus on the detection and characterization of ADAs**. Data on the incidence, titer, persistence, and neutralizing capacity of ADAs should typically be obtained… **The correlation between ADA development and PK/PD, efficacy, and safety** should always be investigated

”

NMPA

“

Most of the adverse events resulting from elicitation of an immune response to a therapeutic protein product appear to be mediated by humoral mechanisms, **circulating antibody to the therapeutic protein product has been the chief criterion** for defining an immune response to these products.

”

FDA

“

FDA believes that having **a dedicated subsection (i.e., 12.6. Immunogenicity)** under the CLINICAL PHARMACOLOGY section allows a consistent location for **summarizing data on anti-drug antibody incidence and its pharmacokinetic and pharmacodynamic effects.**

”

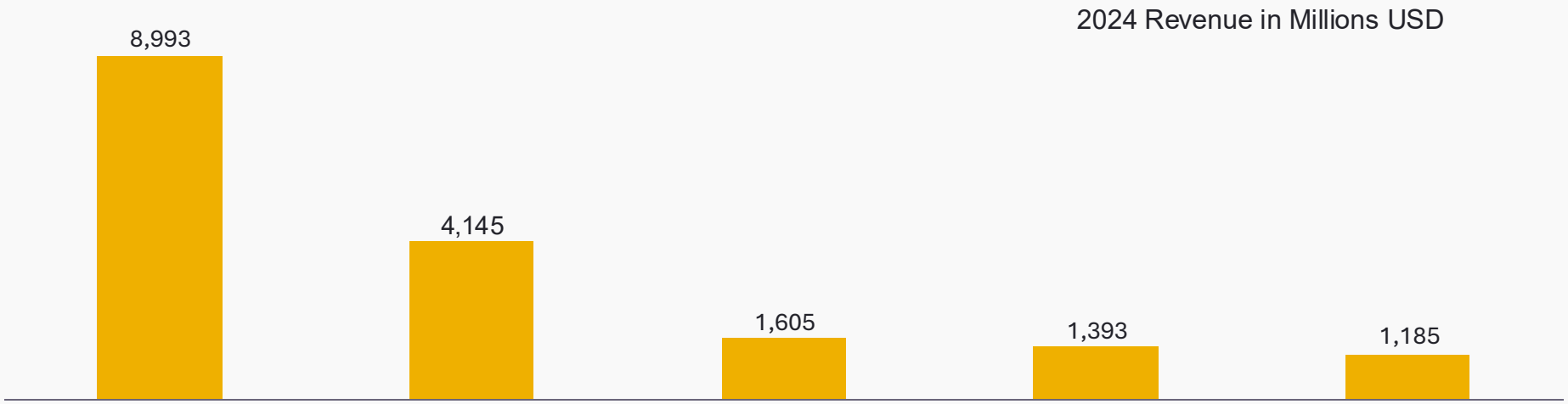
FDA

Source：NMPA, FDA

AdaMunix

ADAs Negatively Impacted Approved Therapeutic Agents

Billions in annual revenue lost due to termination of drug development or discontinuation of therapies



Product	Humira	Tecentriq	Remicade	Myozyme/Nexviazyme	Krystexxa
Target	TNF-α antibody	PD-L1 antibody	TNF-α antibody	Enzyme replacement	Enzyme
Approval	2002	2016	1998	2006	2010
Company	Abbvie	Roche	J&J	Sanofi	Amgen
ADA Rate	**20-40%**	**30-48%**	**60%**	**90%**	**92%**

Source: Company annual report, Research paper

AdaMunix

Adaptive Immune System: B Cells

Essential for host immunity against infection and cancer

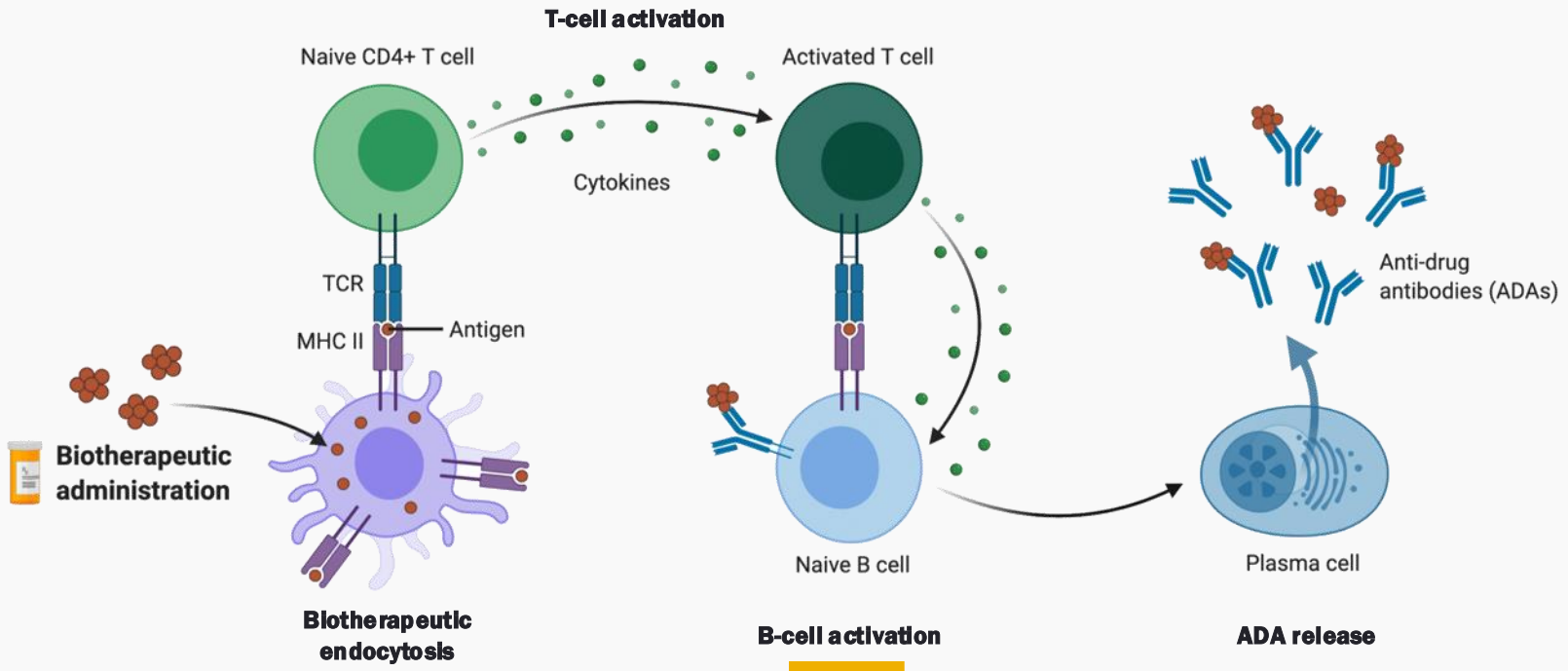
Root cause of many autoimmune diseases

Generates anti-drug antibodies compromising treatment

AdaMunix

Therapeutic Strategy

To improve patient treatments by ablating specific B cells producing ADAs against biologic therapies



AdaMunix's unique technology: Ablating ADA-producing B cell

Technology Platforms

BCR-X: Drug replacement platform

- **Paradigm-breaking ADA-stealth** protein therapeutics
- Safer, more effective, and suitable for long-term use
- Practice changing and product replacement
- Applicable for multiple disease categories

ADA-X: Drug improvement platform

- Prevents ADA and Drug Resistance for **Approved Therapeutics**
- Through combinations with approved drugs, specifically eliminates ADA while preserving the host's immune function
- Strengthens barriers and enable life cycle management

AdaMunix

BCR-X: New Generation of ADA-stealth Protein Therapeutics

Paradigm breaking design for protein drugs that are predicted to be devoid of ADAs

Positioning

- **Replace current protein therapeutics** that may lose clinical efficacy or induce safety issues due to the production of ADAs, known as "inhibitors."
- By avoiding ADA, BCR-X products would be safer, more effective and can be used for longer durations

Business model

- Develop **new generations of protein drugs**
- Licensing to or co-development with other pharma

AdaMunix

BCR-X Platform – Progress Update

Developed a new technology platform to ADA-stealth drug to replace ADA-prone drugs

Lead compound identified for nextgen uricase

Multiple provisional patents filed for nextgen ADA-stealth drugs

AdaMunix

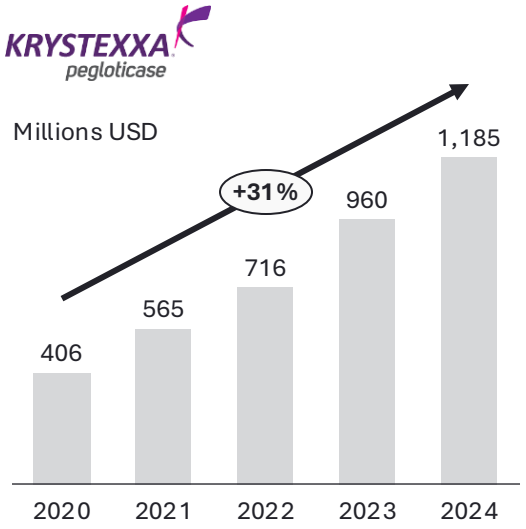
A Partial List of Lead Drugs to Be Replaced by BCR-X

Drugs	Company	ADA rate	ADA impact	Sales
Palynziq	BioMarin	100%	PK, lost of drug activity and hypersensitivity reaction	$ 500-700 million
Krystexxa	Amgen (Horizon)	90% ADA (47% high)	Inactivation	$ 1.2 billion
Elaprase	Takeda	50-68%	Anaphylaxis, PK	$ 1.2 Billion

AdaMunix

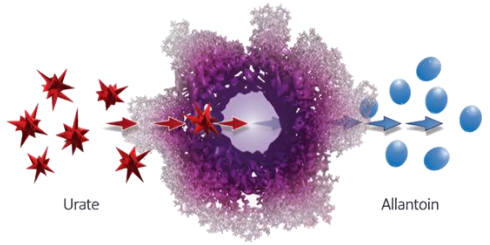
Uricase: Highly effective but challenged by ADA

KRYSTEXXA



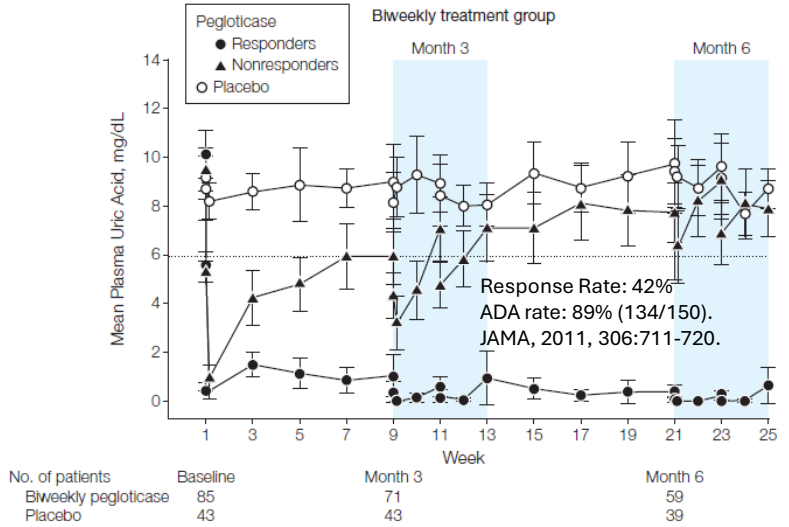
- KRYSTEXXA is the only FDA-approved treatment for out-of-control gout, and it's approved to be given with methotrexate

Clear MoA



- KRYSTEXXA is a pegylated, recombinant porcine-like uricase enzyme
- Uricase converts uric acid into more soluble allantoin for excretion.
- While some animals produce uricase naturally, humans lack it due to a genetic mutation.

For Responders, Efficacy is Outstanding



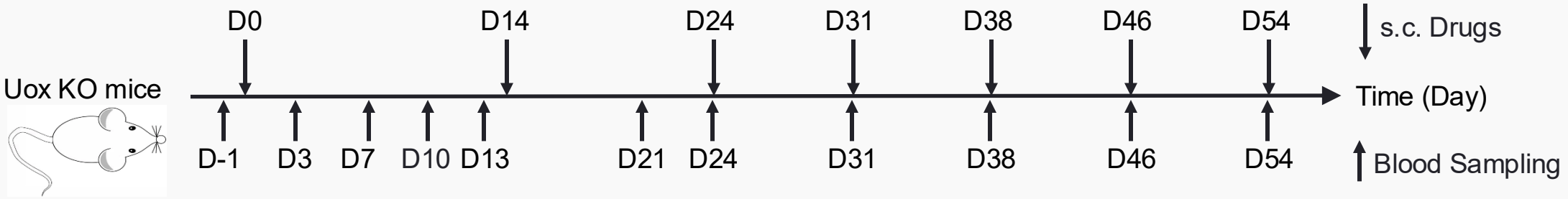
Source: MIRROR RCT

AdaMunix

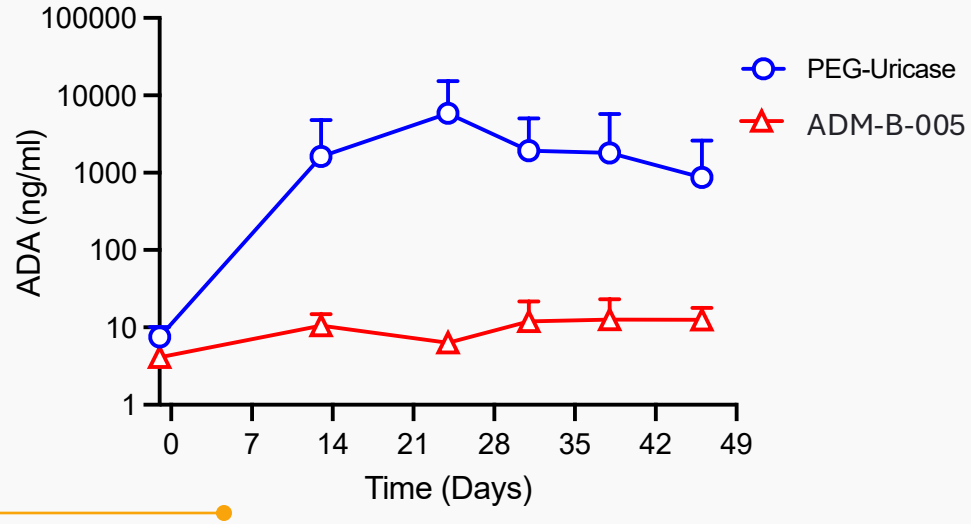
Preclinical Proof-of-Concept (S.C.)

ADA-stealth ADM-B-005 enables subcutaneous injection for gout therapy

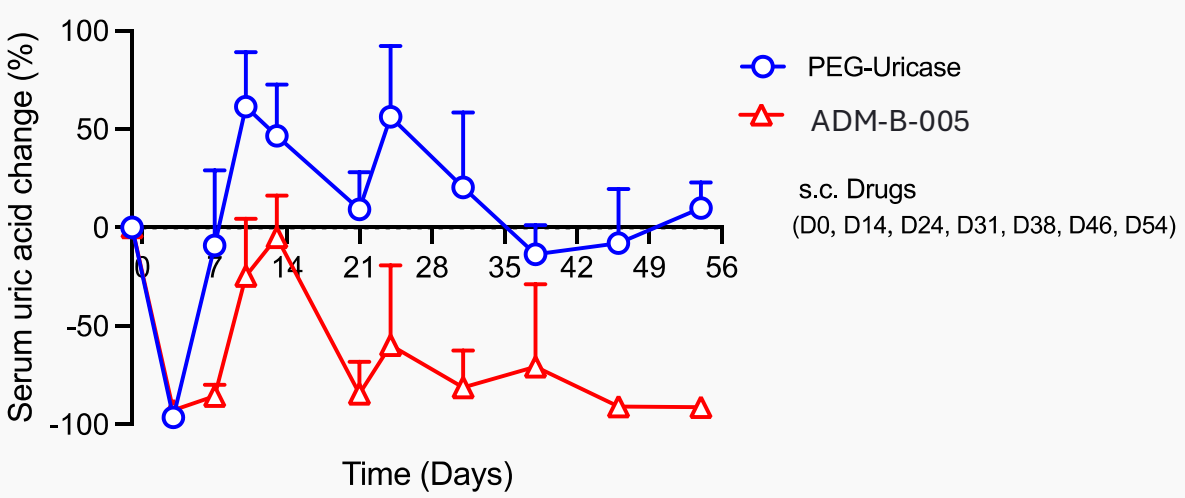
A



B



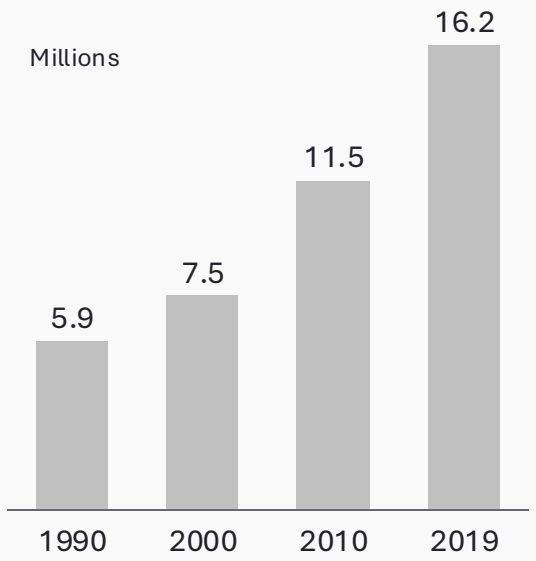
C



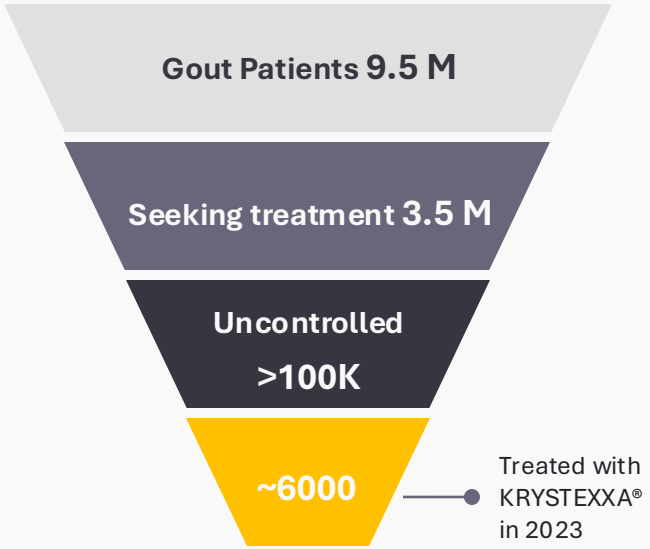
AdaMunix

Huge Market Opportunity for ADM-B-005

China - Over 16 M Patients



U.S - 9.5 M Patients, >100K uncontrolled



- ADM-B-005 have the potential to overcome the ADA issue
- **Drug profile**: 100% response rate, with no infusion reactions, more convenient, long-term use
- Strong potential to become the 2nd-line or even 1st-line therapy.

Source: Global Burden of Disease; Amgen Presentation

AdaMunix

Competitive Landscape

ADM-B-005 is expected to become the world's first next generation drug

	Product	Stage	Company	Note
Global	Pegloticase（Krystexxa）	Approved	Amgen/Horizon	1.2 billion USD in sales by 2024
	SEL-212	NDA	Selecta/SOBI	General immune suppression, similar performance as Krystexxa
	PRX-115	Phase I	Protalix	2024/10 published Phase I data, design similar to Krystexxa
	ProGly-Uricase	Pre-clinical	GRO Bio	2024/07 B round $60M financing, program closed March 25 due to poor preclinical efficacy
China	PEG-Uricase	Phase II	Xiuzheng Pharmaceutical	Similar strategy as Krystexxa
	HZBio1	Phase II	Grand Pharmaceutical	Similar strategy as Krystexxa
	JS103	Phase I	Junshi Biosciences	2021/05 IND approval, inactive
	SIBP-R002	Phase Ib	SIBP CNBG*	Similar strategy as Krystexxa
	F012	Phase I	Shandong New Time Pharma	Similar strategy as
	Pegadricase	Phase I	3SBio	Inactive

* SIBP CNBG (Shanghai Institute of Biological Products Co., Ltd.)

Source：Pharmacodia Database, Public Information

AdaMunix

Highlights of ADM-B-005

- Huge commercial opportunity
- Clear mechanism of action
- **High translatability from animal to human**
  - Uricase is a molecular with no species difference, efficacy could be confirmed in preclinical animal studies
  - ADA elimination results in mice and monkeys will significantly boosts our confidence for clinical results
- **Short development duration**. The primary endpoint of Phase 3 pivotal trial is the response rate during 6 months.
- **Low development cost**. Phase 3 trial sample size is small, only ~150 patients
- **Competition landscape**. No next-generation products are in clinical trials globally
- ADM-B-005 is the **most advanced** next-generation uricase
  - Does not induced ADAs, could be long-term administered
  - the only one can be administered by S.C.

AdaMunix

ADA-X: Therapeutic Agents

The first-and-only targeted solution to drug-specific ADA for therapeutic agents

Positioning

- **Improving a group of drugs** (branded drugs and biosimilars) , can be positioned as an essential treatment for enhanced clinical benefits
- Boosting efficacy and reducing AEs of specific drugs, can **extend exclusivity and build a competition barrier for blockbuster drugs**

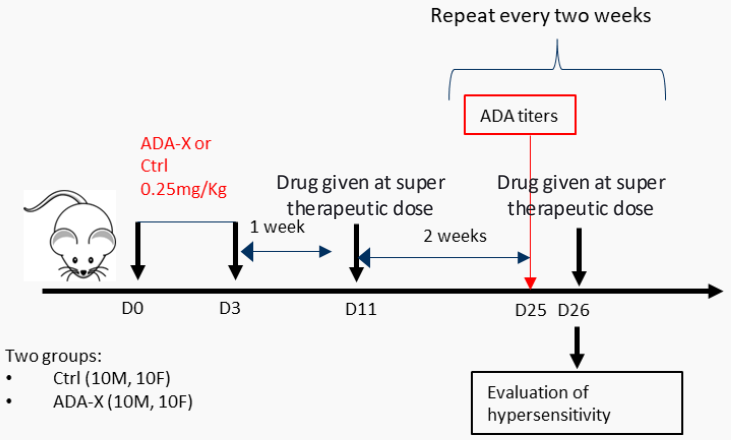
Business model

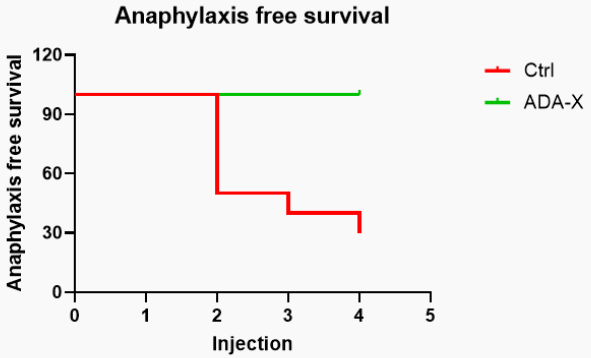
- **License product-specific agents** to pharma
- For drugs that require longer development, with well-established distribution channels, and need to fend off biosimilar competition
- Prototypes of multiple drugs can be developed in 6 months

AdaMunix

Proof-of-Concept Data

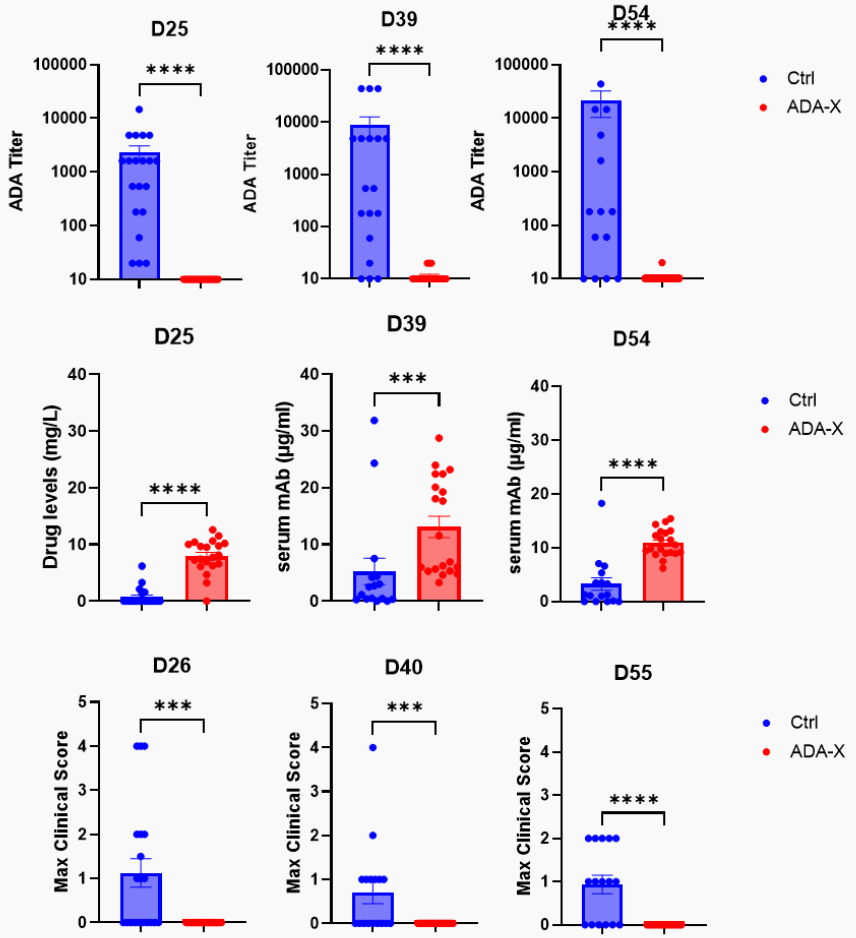
Ablating ADA by the ADA-X platform increases concentration and prevents anaphylaxis





at risk

Injection	0	1	2	3	4
Ctrl	20	20	20	10	8
ADA-X	20	20	20	20	20



ADA-X Platform – Progress Update

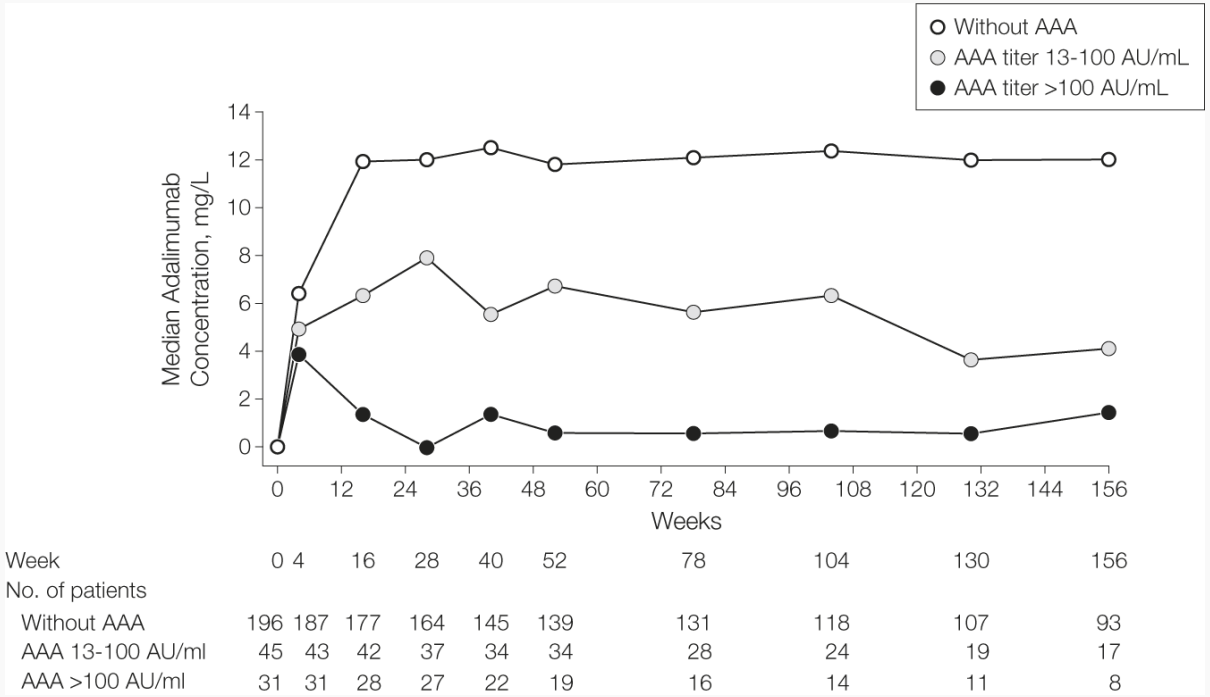
Developed a new technology platform to eliminate ADAs against new drug candidates and approved therapies

Filed multiple provisional patents protecting technological platform and methodology

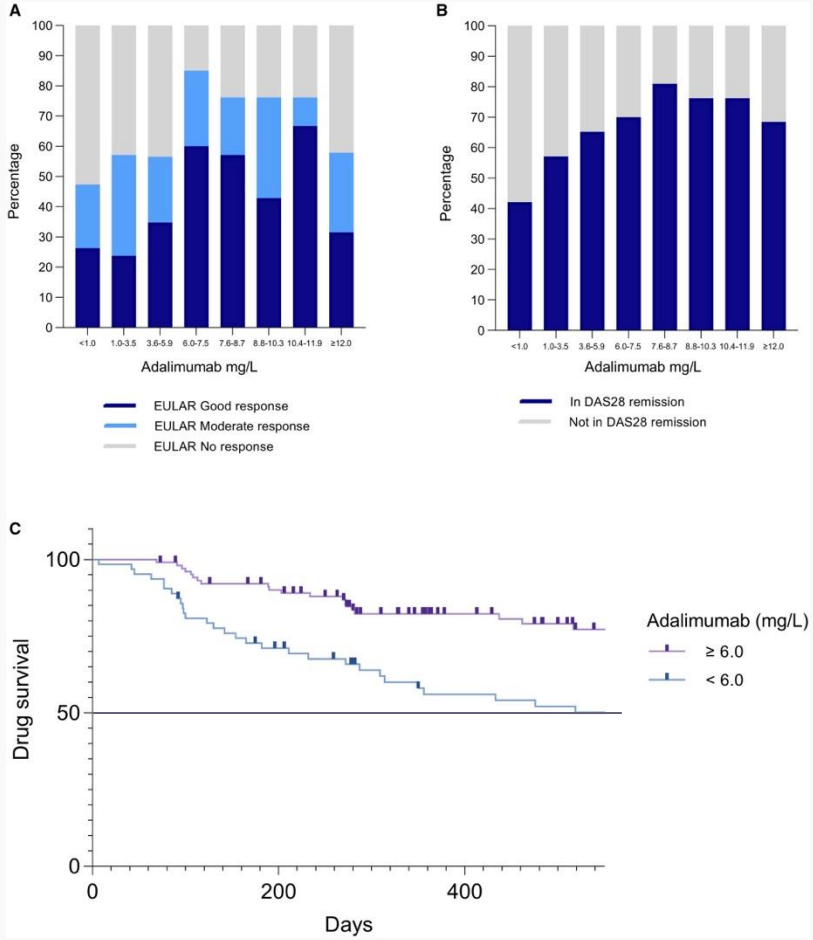
Lead compounds identified that prevent ADA for top selling antibodies

AdaMunix

ADA barrier for Humira



Week	0	4	16	28	40	52	78	104	130	156
No. of patients										
Without AAA	196	187	177	164	145	139	131	118	107	93
AAA 13-100 AU/ml	45	43	42	37	34	34	28	24	19	17
AAA >100 AU/ml	31	31	28	27	22	19	16	14	11	8

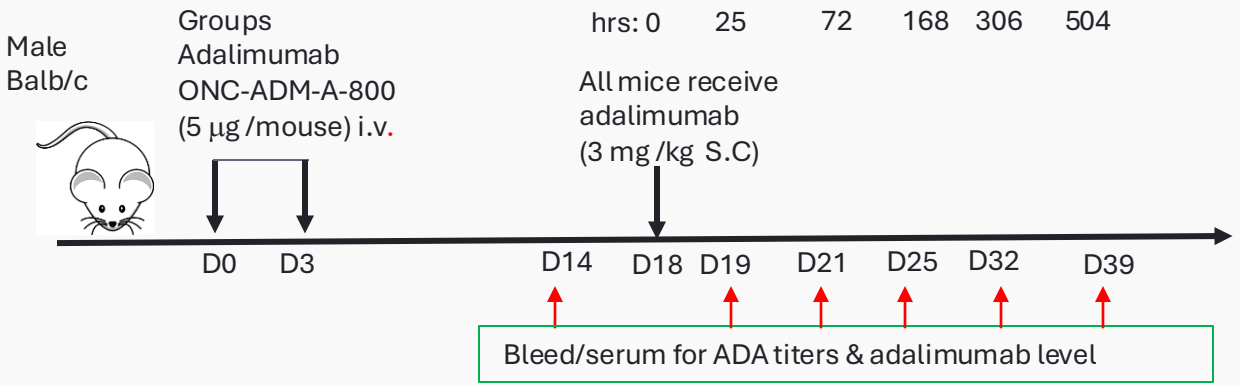


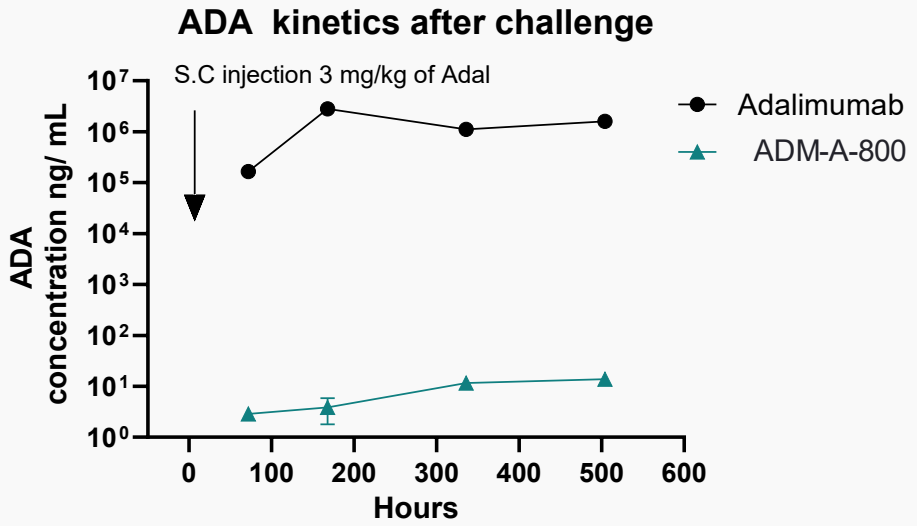
Development of Antidrug Antibodies Against Adalimumab (AAA) and Association With Disease Activity and Treatment Failure During Long-term Follow-up | Rheumatoid Arthritis | JAMA | JAMA Network

Rheumatology (Oxford), Volume 63, Issue 6, June 2024, Pages 1746–1755

AdaMunix

Preclinical proof of concept: prophylactic activity of ADM-A-800

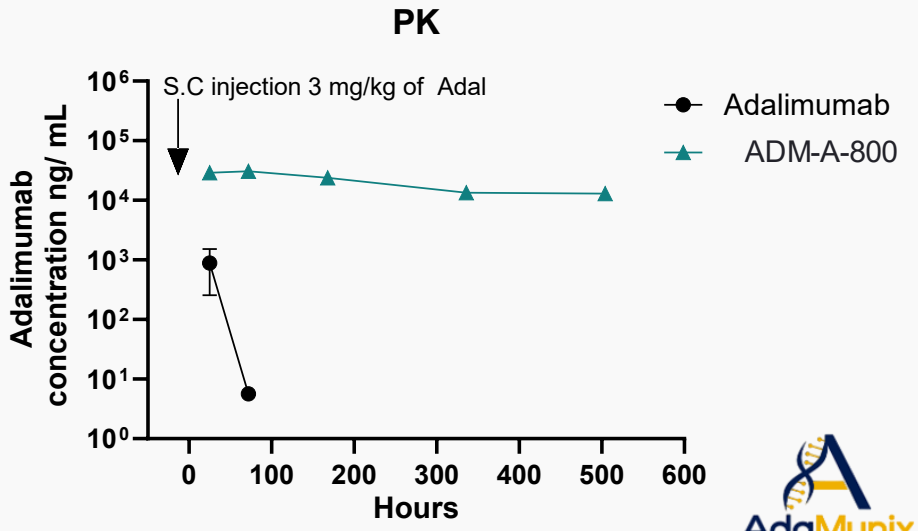




Compared that with adalimumab, ADM-A-800 prophylaxis

- Reduced ADA levels by 100,000 folds
- Increase drug exposure by 103 folds

Pre-treatment	Adalimumab Ctrl	ADM-A-800
C_{Max}(µg/ml)	0.88	29.2
AUC (µg/ml*Hours)	88.5	9,132.3
Half-life (Days)	n.d.	17.3



AdaMunix