SYNACT PHARMA

INFLAMMATION RESOLUTION

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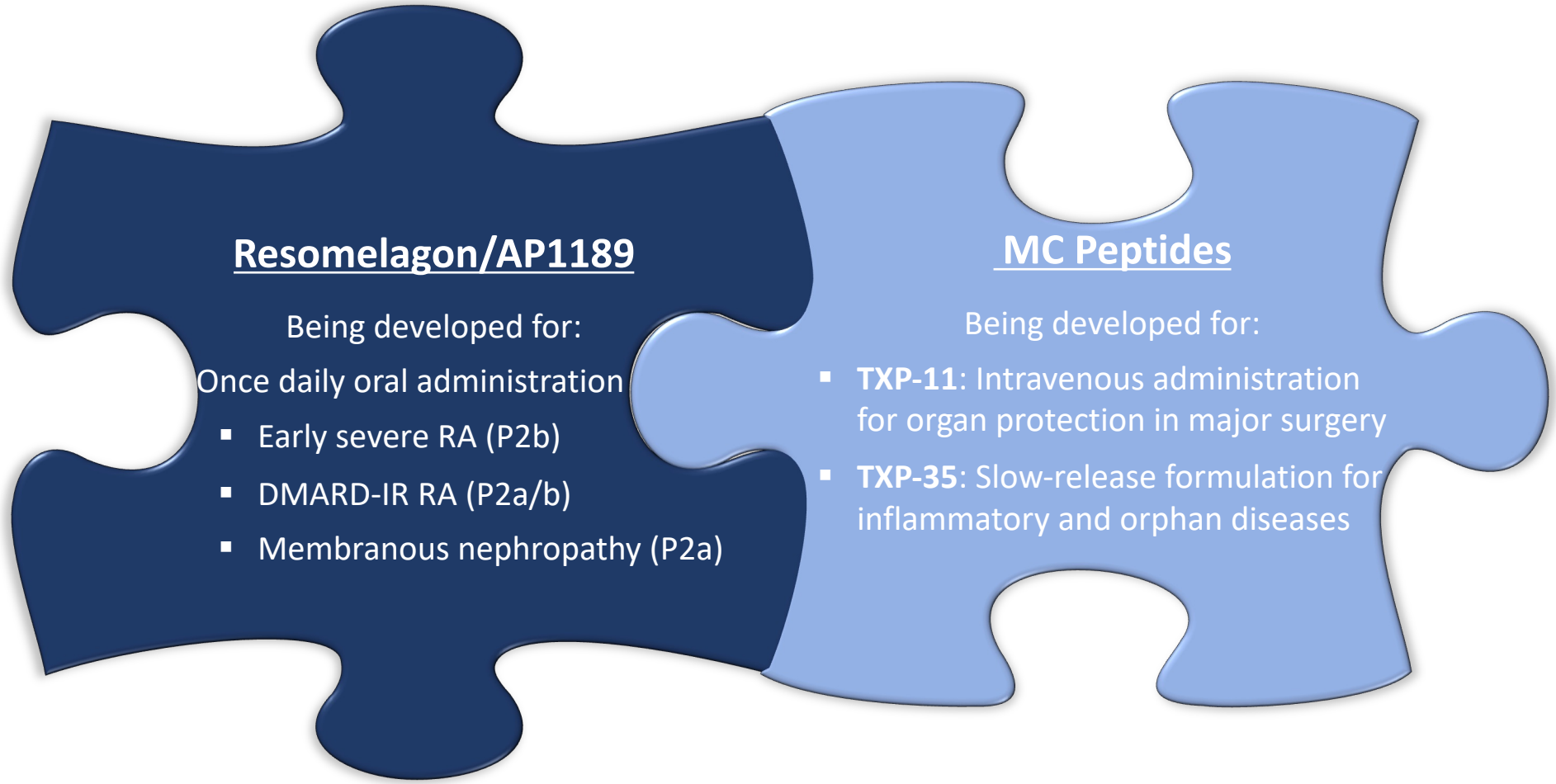
The melanocortin (MC) Peptide program

Combined MC technologies provide versatility to address a broad range of autoimmune and inflammatory diseases

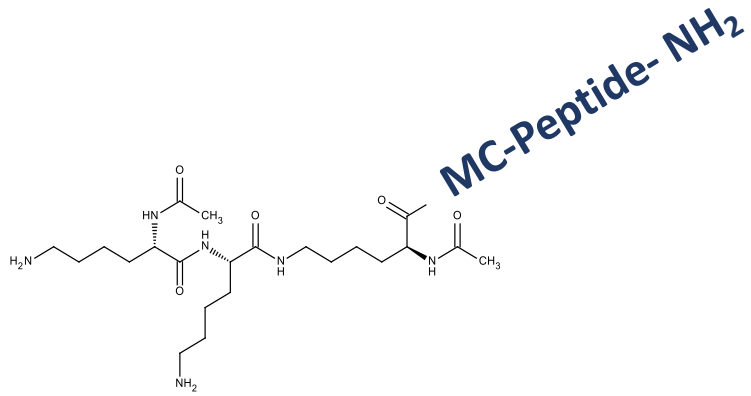


AP1189 and MC peptide agonists are complimentary

	AP1189	MC Peptides
API	• **Small molecule**	• 70+ peptide analogs
Receptor Selectivity	• **Selective for MC receptors 1&3**	• **Varying profiles of MC receptors 1,3,4 & 5**
Agonism	• **Biased Agonist** - Stimulates ERK1/2 activation pathway • Provides immunomodulation without potential cAMP pathway side effects like melanogenesis	• **Full Agonist** – Stimulates both cAMP and ERK1/2 pathways, similarly to natural agonists • Potential to provide additional activity from cAMP stimulation
Dosage Form	• **Oral, once-daily dosage form**	• **IV and Sustained-release SC** • Can develop additional forms per need
Suitable For	• Early use in inflammatory conditions like RA where MC receptors 1&3 are involved and where oral convenience and good tolerability are important • **Combination use with advanced therapies** in patients with more advanced disease	• **IV for severe inflammation** associated with organ dysfunction/failure like major surgery • **Sustained-release SC in inflammatory conditions** where parenteral administration or local administration are desirable

The combined melanocortin technologies will allow targeted development for a wide range of autoimmune and inflammatory diseases with unique assets with MC receptor profiles and routes of administration tailored to the disease and target patient population

BAP modification of MC peptides is associated with increased binding affinity and potency over native ligands



Peptide Agonist	MC1R			MC3R			MC4R			MC5R		
	K_i (nM)	EC_{50} (nM)	E_{MAX} (%)	K_i (nM)	EC_{50} (nM)	E_{MAX} (%)	K_i (nM)	EC_{50} (nM)	E_{MAX} (%)	K_i (nM)	EC_{50} (nM)	E_{MAX} (%)
α-MSH derived:	4.6	13	96	114	62	95	128	28	107	404	1104	103
TXP-11	1.2	8.9	102	24	53	110	26	18	70	193	625	111
NDP-α-MSH derived:	1.8	11	88	21	17	92	11	1.3	100	7.5	40	28
TXP-35	0.29	2.1	90	2.8	1.7	85	2.7	2.6	78	4.3	4.8	29
TXP-59	0.49	1.4	84	2.7	1.6	93	2.4	0.57	69	113	163	11

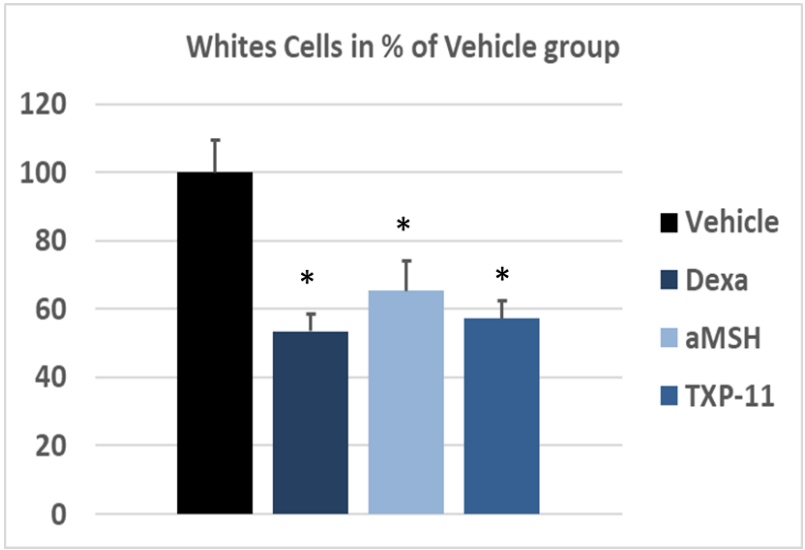
Anti-inflammatory effects of SynAct Pharma´s BAP-modified Melanocortin receptor agonists

Inhibition of inflammatory responses in murine macrophages

	IL-1β	IL-6	TNF-α	CCL-2
αMSH backbone				
TXP-11	76%	80%	62%	16%
TXP-35	71%	72%	52%	33%
γMSH backbone				
TXP-01	80%	86%	72%	49%
TXP-44	76%	74%	66%	42%

Zymosan induced inflammation in murine macrophages-
maximal inhibitory response relative to vehicle treatment

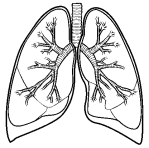
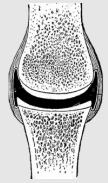
Treatment effect in model of acute peritonitis



Compounds given iv; n=18 per group
Mean ±SE. *: p<0,01 vs vehicle

Data on file

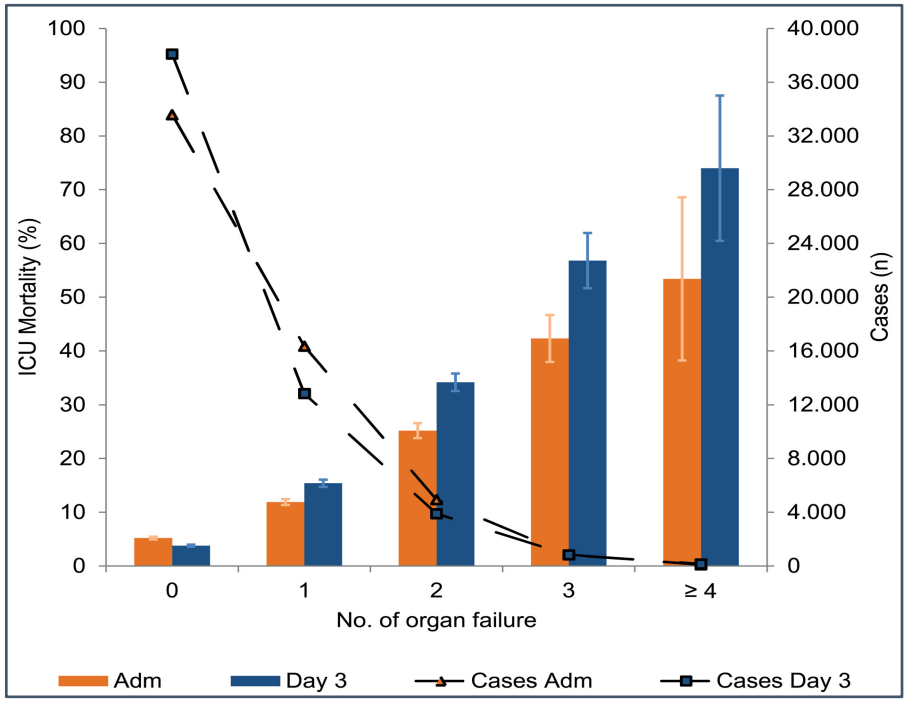
Peptides to target high unmet needs and high value opportunities

Therapeutic Area	Evidence for Targeting With Melanocortin agonists	Development Strategy
 **Critical Care**	▪ αMSH has demonstrated organ protective effects in several models of systemic inflammation ▪ An αMSH analogs demonstrated activity in preventing the need for RRT in CABG surgery patients ▪ Wealth of animal modelling data on αMSH and analogs	▪ Short-term dosing, IV administration and ability for multiple daily doses provide quick straightforward path to clinic ▪ Ability to target multiple organs/systems including pulmonary, cardiac and renal
 **Rheumatology**	▪ Complete melanocortin system is expressed in joints ▪ Demonstrated Acthar efficacy in RA, PSA, lupus, ankylosing spondylitis and myositis ▪ MC1R and particularly MC3R are believed to be the key MC receptors in the osteoarticular system	▪ Numerous large and orphan diseases shown to be responsive to melanocortins are treated by rheumatologists ▪ Diseases are addressable with subcutaneous administration
 **Ophthalmology**	▪ αMSH is constitutively expressed in eye and has immunomodulating effects on retinal cells ▪ Acthar demonstrated efficacy in refractory uveitis ▪ Positive P2 data form competing technology in dry-eye disease (DED)	▪ Large disease conditions like dry eye disease are accessible via eye drops - quicker path to clinic ▪ Both orphan (non-infectious uveitis) and large (AMD) diseases can be targeted with SC

May establish collaborative efforts in additional therapeutic areas like pulmonary and dermatology

Postoperative organ dysfunction and failure is a significant source of in-hospital mortality and healthcare system cost

Postoperative Organ Dysfunction/Failure and Associated In-Hospital Mortality From a German National ICU Registry[2]				
Surgery	**Status**	**Pulmonary**	**Cardiac**	**Renal**
Scheduled	Dysfunction	83%	53%	30%
	Failure	12%	40%	5%
Unscheduled	Dysfunction	85%	56%	36%
	Failure	19%	38%	8%



Postoperative Organ Dysfunction and Failure

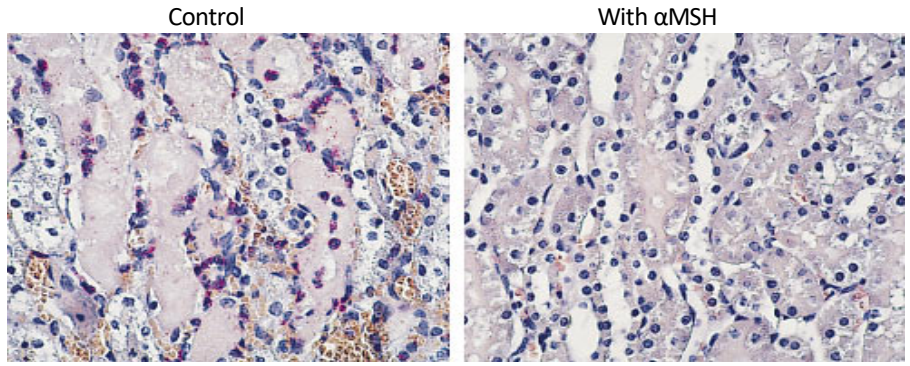
- Organ dysfunction and failure are common surgical complications[1]
- The three primary organs/systems involved in perioperative complications include the pulmonary cardiac and renal systems
- In-hospital mortality from surgical-admissions to the ICU was shown to increase substantially with the number of impaired organs (SOFA Score)
- For postsurgical patients the risk of in-hospital mortality was highest for liver, renal and pulmonary with odds ratios of ~3.1, 2.7 and 2.3 respectively in patients with an ICU LoS > 5 days

[1] Bingold, et al. (2015) Individual Organ Failure and Concomitant Risk of Mortality Differs According to the Type of Admission to ICU. PLoS ONE 10(8); [2]Figure from and data table adapted from same

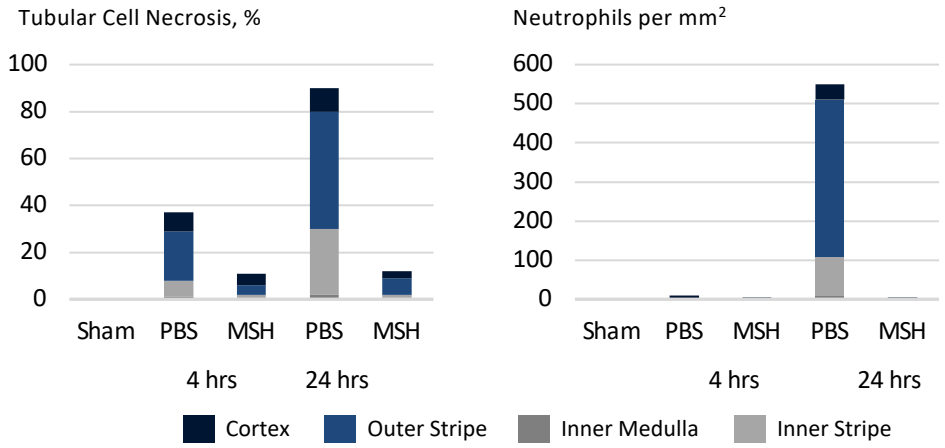
Melanocortin peptide agonists in disease models – marked treatment potential in therapeutic dose regiment

αMSH is kidney protective in a rodent model of ischemic AKI

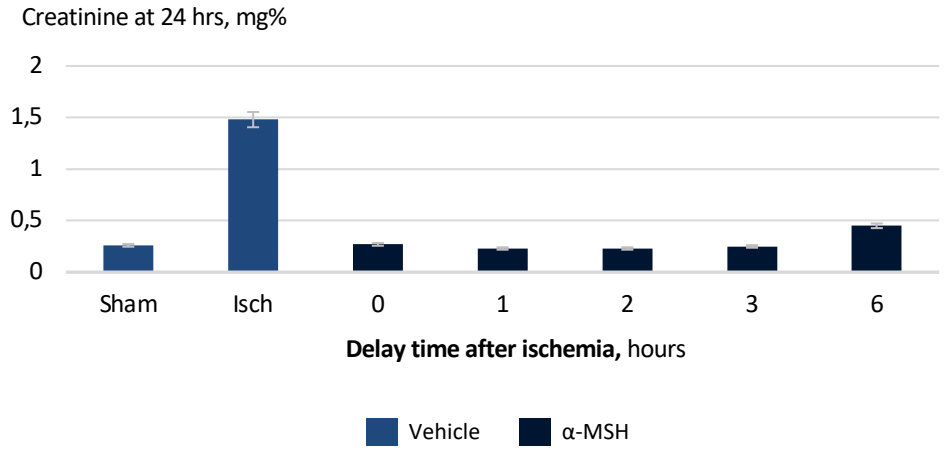
Mice were subjected to bilateral renal ischemia and the first dose of αMSH was given at time 0 or was delayed from 1-6 hours after reperfusion. All groups received subsequent doses at 6 and 16 hours after clamp removal.



Significant reduction in the extent of tubular infiltration



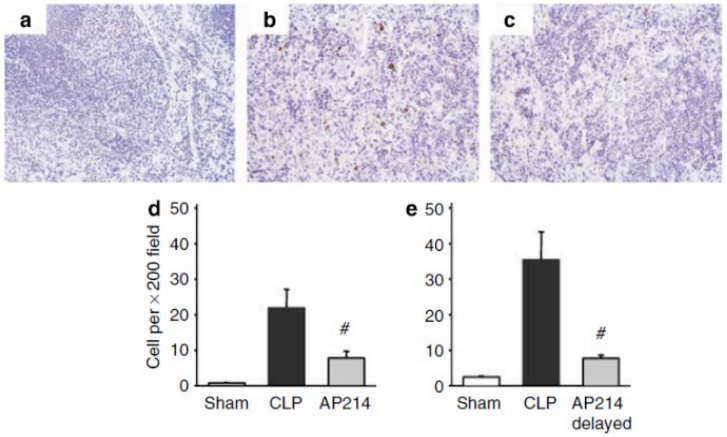
Significant decrease in serum creatinine



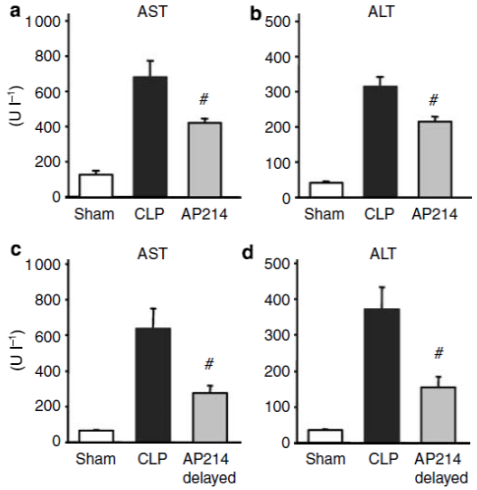
JCI 1997; 99:1165-72

Marked organ protective effects of the AP214 melanocortin peptide agonist in model of Sepsis

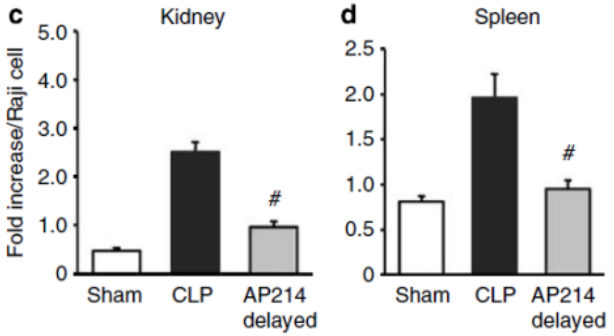
Reduces Splenic Caspase 3 activation



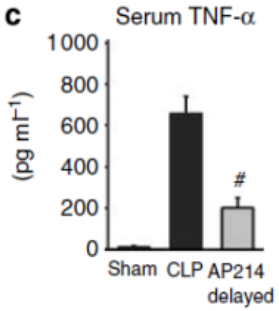
Reduces liver affection



Reduces NF-kB activation



Reduces circulating levels of TNF-α



Sepsis were induced in mice by caecal ligation puncture (CLP) and treatment with TXP-1214 (AP214) were given 6 hours later)- Readout collected 24 hours following CLP. Animals were co-treatment with imipenem/cilastatin

Kidney Int. 2008; 11:1266-74

TXP-11 is advancing to Phase 1 clinical development in H1 2024 – Targeting organ dysfunction following major CV Surgery

- **Lead candidate in novel class of melanocortin receptor agonists with increased affinity and potency compared to native melanocortins**
- **Peptide designed by use of IP-protected BAP (Branched Amino-acid Probe) technology**
- **Anti-inflammatory and pro-resolving effects in relevant experimental models**
- **TXP-11 is being developed as an intravenous solution for the treatment of organ dysfunction as seen in major surgery and in critical care patients**
- **Preclinical development including IND enabling tox and GMP production of study medicine has been completed**
- **Continued supportive pharmacology program to support CTA is ongoing**
- **Current development status:**
  - Pharmacology program in additional disease models ongoing
  - toxicology and safety pharmacological studies to support clinical development completed – NOAEL: rat: 25 mg/kg given once daily for 2 weeks ; minipig: 10 mg/kg given as 30 infusion once daily for 2 weeks.
  - CMC development for Phase 1 and 2a studies completed. This includes GMP produced drug substance and production of first clinical batch of drug product

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Thank you

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Q&A